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# Lindane: Position Document 4

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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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# EXECUTIVE SUMMARY

In July 1980 the Environmental Protection Agency issued Lindane Position Document 2/3 (PD 2/3) which proposed to cancel most of the uses of the insecticide lindane (45 FR 45362). The proposal was based on a riskbenefit determination which suggested that the risks considerably outweighed the benefits associated with lindane's continued use.

This document, Lindane Position Document 4, presents EPA's final determination on lindane. It is based on a revised analysis of the risks and benefits, following careful consideration of the comments EPA has received from the Scientific Advisory Panel, the U.S. Department of Agriculture, members of the affected industries, and the general public.

The decision described in this document is quite different from the 1980 proposed decision. EPA originally planned to cancel all of lindane's uses except for the commercial ornamental, livestock, and dog wash uses. The final decision is to continue registration of most uses of lindane. The Agency will cancel the indoor uses of smoke fumigation devices and the use of dog dips to control pests other than mites. All other uses of lindane will be continued with various restrictions. These restrictions vary according to the degree of hazard associated with the use, but typical requirements include protective clothing, label statements describing necessary precautions, and restriction of some uses to certified pesticide applicators.

The many reasons for these changes are discussed in detail in the body of this document. However, there are five primary considerations which caused EPA to revise its proposed decision.

First, the Scientific Advisory Panel (SAP) disagreed with many of the regulatory positions proposed in the PD 2/3. Because of the position taken by the SAP, the Agency undertook a thorough reevalution of the analysis and regulatory position proposed in the PD 2/3.

Second, the exposure estimates used in the original analysis were purposefully conservative, since they were based on a paucity of information. EPA prefers in such cases to err on the side of safety. Since the proposed decision (PD 2/3) was published, EPA has been able to improve its risk estimates significantly. Some of the revisions are based on new, more detailed use information, including the routine use of protective clothing for some uses. Others are based on the use of better surrogate data. Details of all the changes in the exposure analysis, and the reasons for them, may be found in Appendix III.

The third reason for the revised decision is that EPA's assessment of the possible risks from lindane, particularly the potential cancer risks, suggest that the available information is not sufficient to support cancelling the use of lindane. This conclusion is based on a combination of three key considerations: 1) evidence regarding the magnitude of the potential cancer risk to humans is limited; 2) most of the cancer risks (which are conservative estimates) can be acceptably reduced by less stringent measures than cancellation; and 3) potential risks to the exposed populations from leaving lindane on the market while additional testing is done are not estimated to be significant. Even the possible risks from a working lifetime of exposure, as estimated in this document, are in most cases adequately low. Further discussion of the details of cancer risk considerations, and the Agency's decision on how to deal with the many uncertainties surrounding this issue, may be found under "II. A. The Presumption of Oncogenicity".

Fourth, the Agency has reevaluated the issue of fetotoxic effects, the comments received on this subject, and the animal studies showing such effects. Effects on reproduction are of concern to the Agency; however, their toxicological end point must be considered in relation to other toxicological effects. The fetotoxic effects of lindane only occur at exposure levels above those showing maternal toxicity. The Agency, therefore, concludes that the risk reductions discussed in PD-4 (labelling, restriction of use to informed persons) will concommitantly and sufficiently reduce the risk of fetotoxicity.

Fifth, the notable benefits of lindane's use are given more appropriate consideration in the final decision, as was suggested in the many comments which the Agency received. The decision proposed in 1980 was criticized by the U.S. Department of Agriculture and the public, for not adequately considering ways to reduce the risks through less stringent measures than cancellation. The Agency agrees that the benefits were not adequately considered in its original assessment, and has revised the risk/benefit analysis accordingly.

In conclusion, this final decision on the pesticidal uses of lindane is based upon better information and consideration of the reasonable regulatory options short of cancellation. The final decision has been carefully designed to insure that immediate but minimally burdensome steps will be taken to reduce the potential risks to exposed populations. At the same time, this decision preserves the benefits of lindane's use while ensuring that uncertainties surrounding some of the risks will be reduced within a reasonable time frame.

A three month, subchronic oral feeding study in rats recently submitted to the Agency indicates a NOEL of 0.3 mg/kg/day with kidney damage at the next highest dose. In order to properly evaluate this study it will be necessary for the Agency to thoroughly review the complete subchronic and chronic data base, which was not done as part of this RPAR. The Agency has decided not to delay the issuance of the PD 4 because it does not want to delay the implementation of the protections to the environment contained in the regulatory measures in the PD 4. However, the Agency will give high priority to the development of a Registration Standard for lindane which will include a complete review of lindane's general toxic effects.

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# I. INTRODUCTION

The U.S. Environmental Protection Agency (EPA or Agency) regulates all pesticide products under authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended ( 7 U.S.C. 136 et seq.). Section 6(b) of FIFRA authorizes the Administrator of EPA to issue a notice of intent either to cancel the registration, or to change the classification of a pesticide product if in his judgement either the pesticide or its labeling does not comply with the provisions of FIFRA, or causes unreasonable adverse effects to human health or the environment.

EPA designed the Rebuttable Presumption Against Registration (RPAR) process, described in 40 CFR 162.11, to gather and analyze data on the risks and benefits of pesticides, and to allow all interested parties to participate by submitting information relevant to the Agency's presumption. The RPAR process may be initiated against any pesticide which the Agency has reason to believe may cause unreasonable adverse effects. This determination is typically based upon a finding that the pesticide meets or exceeds certain "risk criteria", which are defined in the regulation (ibid.).

In the FEDERAL REGISTER of February 17, 1977 (42 FR 9816), EPA published an RPAR notice for pesticide products containing lindane. It cited three risk criteria which lindane met or exceeded: oncogenic effects (40 CFR 162.11 (a) (3) (ii) (A)), reproductive and fetotoxic effects (40 CFR 162.11 (a) (3) (ii) (B)), and acute toxicity to aquatic wildlife (40 CFR 162.11 (a) (3) (i) (B) (3)). Additional concerns for which the Agency requested information were: population reduction in avian wildlife, acute hazards to humans and domestic animals, hematoxic effects (blood dyscrasias) in humans, mutagenicity and isomerization (several other isomers of benzene hexachloride are known to be oncogenic).

On July 21, 1978, EPA announced in the FEDERAL REGISTER that it had asked registrants of benzene hexachloride (BHC), which contains lindane and other isomers, to amend their registrations. Specifically, BHC registrants voluntarily agreed to eliminate from their formulations the alpha and beta isomers of BHC, which are established carcinogens, and to substitute lindane. Lindane is by far the most insecticidally active BHC isomer, and must be at least 99% pure gamma isomer for purposes of registration with EPA. The substitution plan eliminated the use of BHC products in the United States. The amended lindane-containing products were then subject to the lindane RPAR. The regulatory decision described in this document is therefore based on test data for 99% or greater gamma isomer of BHC, and should not be construed to apply to BHC or to products containing greater than one percent of the other BHC isomers.

Following the 1977 RPAR announcement, EPA reviewed comments ("rebuttals") from affected parties, and analyzed the human and environmental risks and benefits of lindane's pesticidal uses. A preliminary regulatory decision ("Preliminary Notice of Determination") was published in the FEDERAL REGISTER of July 3, 1980 (42 FR 45362). The basis and details of the preliminary decision were described in Lindane Position Document 2/3 (PD 2/3) (EPA, 1980a). The PD 2/3 described and incorporated the comments received since the lindane Position Document 1 (PD 1), and presented the course of action the Agency proposed to take, based on an analysis of the risks and benefits of representative uses of lindane. *

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* The human pharmaceutical use of lindane for treatment of lice and scabies was not included in the Agency's assessment since it has been under the jurisdiction of the U.S. Food and Drug Administration since 1979 (44 FR 63749).

of this document, according to their content.

This document is organized as follows: Chapter I is this Introduction, Chapters II, III, IV and V contain summaries of the comments and information received on the health and environmental concerns, exposure, and benefits of lindane. In each case, EPA provides its analysis of these comments, and a final conclusion. In Chapter VI, EPA summarizes those considerations which were most important in reaching its regulatory conclusions on lindane. These key considerations are then used in the risk-benefit analyses in Chapter VII, which describe the Agency's rationale for the regulatory actions it intends to take. Lastly, Chapter VIII discusses several regulatory actions which will be taken on all the pesticidal uses of lindane, and presents an overview of EPA's decisions for the various use groups. Explanations of the differences in the PD 2/3 and PD 4 exposure analyses are described in Appendix III.

All nonconfidential comments received by EPA regarding this document, are available for review in the public file located in the Document Control Office, room 236, 1921 Jefferson Davis Highway, Arlington, Virginia 22202.

A draft of the PD 4 (dated Feb. 23, 1983) was sent to the California Department of Food and Agriculture (CDFA), the Food and Drug Administration (FDA), the Natural Pesources Defense Council (NRDC), the National Audubon Society, five peer reviewers of the former Scientific Advisory Panel, and to the Centre International d'Etudes du Lindane (CIEL) for comments. The Agency has considered these comments and has addressed all substantive issues during its reevaluation and revisions of the PD 4. The comments are each addressed within the appropriate section of this document. Four of the comments (FDA, CIEL, and two peer reviewers) essentially supported the EPA position document 4. Suggestions to improve the conclusions and rationale were considered and are incorporated throughout the PD-4 document. Two commenters (NRDC and the National Audubon Society) basically disagreed with the PD-4 draft, and the Agency's departure from the position taken in the PD 2/3. The Agency believes that this departure is now sufficiently addressed and is based on a re-examination of the benefits of lindane, a more precise exposure determination, and a reevaluation of toxicity studies. Three peer reviewers while basically supporting the PD-4 position, disagreed with the retention of household uses of lindane (i.e., the unrestricted uses). The Agency concludes that because the risk estimates for most of these uses are extremely low, cancellation would be arbitrary and not based on its own scientific conclusions. However, the Agency will cancel the indoor use of the smoke fumigation devices and dog dips for control of pests other than mites because the cancer risk is unacceptable. One commenter (California Department of Food and Agriculture) suggested that the question of lindane's oncogenic potential be reevaluated by a group of experts. The Agency believes that further evaluation by another panel, using the same data base, would not provide any additional information in support of the Agency's regulatory position, nor would it settle the ongoing scientific arguments concerning the severity of lindane's (and other similar chemicals) oncogenic potential. In fact, the Agency concludes that it has used a very conservative approach to estimate the cancer risk of lindane although it is considered a "weak" oncogen by many experts.

# II. HEALTH AND ENVIRONMENTAL CONCERNS

## A. The Presumption of Oncogenicity

### 1. EPA's PD 2/3 Position

In Position Document 1, the Agency announced a presumption of oncogenicity based on three laboratory studies in which lindane caused tumors in mice (Goto et al., 1972; Hanada et al., 1973; and Thorpe and Walker, 1973). After completion of a fourth study of carcinogenicity of lindane in mice by the National Cancer Institute (1977) and a study demonstrating carcinogenicity of 2,4,6-trichlorophenol, a metabolite of lindane, the EPA Carcinogen Assessment Group (CAG, 1979) provided a comprehensive review of the oncogenic effects of lindane based on these and other animal studies, for use in Position Document 2/3. At that time, the quantitative risk assessment for 21 uses of lindane was based on the one-hit model. Using this linear low dose model, the slope factor for lindane was estimated as 0.00732 $(ppm)^{-1}$.

### 2. Comments on EPA's PD 2/3 Position, and PD 4 Final Position

The Centre International d'Etudes du Lindane (CIEL), whose membership is comprised of many of the manufacturers of technical grade lindane, submitted extensive comments to EPA on the PD 2/3. Many of the points raised in CIEL's comments were addressed in the PD 2/3. The following issues were either not raised before, or EPA has since changed its position, therefore they are discussed here (Memo, 1982a).

#### a. Choice of an appropriate risk assessment model

##### i. Comments on EPA's PD 2/3 Position

During the Scientific Advisory Panel (SAP) hearings which followed publication of the PD 2/3 (July 24 and August 13-14, 1980), and also in the submission from CIEL, questions were raised about the choice of an appropriate model for extrapolating risk from animals to humans. The SAP suggested that it would be more appropriate to use several models, to show the possible range of risk, rather than using only the one-hit model. CIEL (Vol. 1, page 38 and Exhibit 7, page 4) stated that the one-hit model "vastly over-estimates the true risk", and proposed using the so-called Weibull model instead. Yet another model, the Mantel-Bryan, was proposed by a third scientist within EPA. A fourth model, the multi-stage, is also a linear model and is generally used by EPA in the absence of another which fits the data better. (Memo, 1982a).

The Paper Products submission (30000/10c #93) raised the possibility of evaluating carcinogens differently if the mechanism can be shown to be epigenetic rather than genotoxic. It was argued that lindane is an epigenetic substance for which it should be possible to establish safe threshold levels.

NRDC (1983) supports the Agency's choice of the linear risk assessment model.

## ii. EPA's PD 4 Position

EPA agrees with the SAP that it is generally preferable to use more than one model to estimate risk, especially when there is substantial uncertainty regarding the choice of an appropriate model. However, as detailed in the CAG memo (1982a), the lindane data are insufficient to make use of the alternate models which have been suggested in this case. In short, the statistical basis necessary to draw up a range of risk estimates for lindane does not exist (Memo, 1982a).

Other considerations also limit the scientific justification for using any model other than the linear low dose model. The following discussion of cancer risk models is extracted from memo (1982a).

The mammalian mutagenicity data are insufficient to resolve whether or not lindane is genotoxic. In fact, it may be that lindane acts both as an "initiator" (by a genotoxic mechanism) and a "promoter" (by as yet unknown mechanisms).

The linear non-threshold dose-response relationship is consistent with the relatively few epidemiological studies of cancer responses to specific agents that contain enough information to make the evaluation possible (e.g., radiation induced leukemia, breast and thyroid cancer, skin cancer induced by arsenic in drinking water, liver cancer induced by aflatoxin in the diet).

In the most complete test yet made of animal carcinogenic dose response relationships [the large scale ED$_{01}$ study of 2-acetylaminofluorene in mice at the National Center for Toxicological Research (NCTR)], the liver tumor response was linear down to the lowest dose tested. However, since the bladder cancer response was non-linear in the same experiments, the ED$_{01}$ study implies that non-linear mechanisms also exist.

Because it had the best, albeit limited, scientific basis of any of the current mathematical extrapolation models, the linear (one-hit) non-threshold model was adopted as the primary basis for risk extrapolation to low levels of the dose-response relationship. Risk estimates using the linear model are regarded as plausible upper-limits, since it is possible that a non-linear mechanism could be occurring, which would make the risk approach zero at sufficiently low doses. Based on the one-hit model and the other procedures for estimating risk at the time of PD 2/3 in 1979, the potency, or slope factor, for lindane was estimated to be $b=0.00732(\text{ppm})^{-1}$.

## 1) Multistage Model

In early 1980, the CAG, following suggestions from outside statisticians and other scientists, modified its procedure for estimating risks. This procedure is documented in the "Notice of Availability of Water Quality Criteria Documents" (Federal Register, Vol. 45, No. 231, Friday, November 28, 1980, Notices p. 1). Rather than extrapolate from the lowest dose, which showed a greater response, as had been the procedure using the one-hit model, the multistage procedure used all data points that fit the model. The extrapolation was based on the largest linear component, which then fit the data. Thus, the multistage model is still linear at low doses. The plausible upper-limit slope factor for lindane based on the multistage model is $b = 0.030\ (\text{ppm})^{-1}$.

## 2) Mantel-Bryan Procedure

EPA has used the Mantel Bryan procedure to estimate lindane risks. This procedure was to start from the only treated dosage group of the Tunstall study (incidence of 27/28 at 400 ppm in diet), calculate the 99% upper confidence limit of this response (which was found to be 99.99% of the animals responding), then use a log-probit slope of 1.0 to extrapolate to low doses. For a 10,000-fold reduction in dose, the risk is estimated to be 16%, whereas the linear multistage model gives 0.12% as the risk. The marked increase of estimated risk (compared to a linear model) results from the extremely nonlinear behavior of the log-probit function at the extreme high end (close to 100% response) of the curve. The practice of taking the upper confidence limit of the high response puts one even further into the non-linear region. If the lindane response had been near 10% rather than 95%, the risk after extrapolating downward by a factor of 10,000 would have been much less than that using the linear model. Thus, results are unreliable if the Mantel-Bryan procedure is used with data such as lindane.

The CAG does not consider this model appropriate for risk estimation for two reasons: 1) the results are highly dependent on where the response data happen to fall in the animal experiment, as explained above; and 2) the results are highly dependent upon the arbitrary slope, which is chosen independently of the data. Mantel and Bryan chose a slope of 1.0 to be "conservative", i.e., to intentionally overestimate risks, so that a small acceptable dose would be chosen, which would be certain to protect public health.

for quantitative risk extrapolation one should use the actual slope determined from the data, which typically ranges anywhere from 1.5 to 5, if one believes that the log-probit model really describes the cancer dose-response relationship. Mantel and Bryan did not intend to use this log-probit model to estimate quantitative risks, merely a "virtually safe dose," below which safety could be assured. The Agency feels that in this case, this approach is unnecessarily conservative.

### 3) Weibull Model

Dr. Frank Carlborg of CIEL uses a generalization of the linear dose-response model in which the dose, x, appears as the $k^{th}$ power. His model, which he calls the Weibull model, is $P(x) = 1 - \exp - (a+bx^k)$. But since lindane was tested at only one dose level in the Tunstall experiment, not enough information is available from that study to estimate a value for k. Therefore, Dr. Carlborg attempts to estimate the k value for lindane by assuming that the k value for lindane is in the same range as that for other hydrocarbons producing liver responses in mice. The k values for nine compounds were found to range between 0.33 and 4.5. Since the largest experiment yet done, (the $ED_{01}$ study by NCTR), gave a k value of 1.49 and since that value is within the range of variation of the chlorinated compounds, Dr. Carlborg assumes this value of k for lindane. To get a value for the slope parameter, b, he used the one-hit slope derived from the Tunstall experiments.

In the opinion of the CAG, he is not justified in first assuming that k = 1.49 to get a value for a one-hit slope, b, and then choosing a different value of k based on other experiments, and incorporating these values into the same model. In the Weibull model these two parameters cannot be independently estimated with any degree of certainty. An examination of Dr. Carlborg's calculation shows such a wide variation in the estimates of both b and k, that virtually any risk estimates would be possible when the Weibull model is used with the lindane data.

### 4) Appropriateness of Various Models for Lindane Risk Assessment

The dose-response data for lindane are very sparse. Only two positive studies have been reported where there is an adequate number of animals for conducting a risk assessment. In one study (Thorpe and Walker, 1973) only one treated dose group was tested, and in the other [National Cancer Institute (NCI)], two doses were used but the highest dose produced a non-significant increase. Thus, there are only two dose-response data points which allow for the estimate of only one parameter. The linear model, which currently takes the form of the linearized multistage model, gives a plausible upper-limit of risk, because most dose-response data appear to be either linear or to have upward curvature, at least in the low dose region. Furthermore, the linearized multistage model is felt to give a more reliable upper-limit risk estimate when the carcinogen is also genotoxic. The Mantel-Bryan procedure in the case of the lindane data is unreliable because the upper confidence limit is so close to an incidence of 1.0 as to make any risk extrapolations unreliable and because the arbitrary slope of 1.0 probit per log dose must be used in the absence of dose-response data. The CIEL "Weibull" approach is simply a selection of the dose slope parameter, k, based on other compounds. Since any value k would fit the lindane data, and a large range of k's fit data on similar compounds, no confidence can be placed on the accuracy of an extrapolation to low doses.

The most commonly accepted mechanism of carcinogenesis is the somatic cell mutation theory, in which the agent causes an alteration in the genetic material of a cell, which is replicated in subsequent generations. This genetic change can arise from a single molecular change in the DNA of a cell with a probability that is proportional to the applied dose.

In conclusion, there is not enough information at this time to justify using any risk model other than one that is linear at low doses. This is the model commonly accepted as valid for providing plausible upper-bound risk estimates. It is also consistent with the commonly accepted mechanism of carcinogenesis: the somatic cell mutation theory.

As discussed in Chapter VII, EPA has taken the uncertainties described above into account in its regulatory decision on lindane. The Agency's decision is specifically designed to reduce the uncertainty within a reasonable time frame, while taking immediate but minimally burdensome steps to protect the populations which may be at risk. These regulatory measures may be revised in the future, if so warranted by significantly improved understanding of lindane's carcinogenic mechanism in animals, or other information relating to its potential to cause cancer in humans. The CIEL and EPA have agreed to the conditions under which additional information (testing) will be obtained. Further details of this agreement may be found in Chapter VII., F.

### b. Use of pooled controls

#### i. Comments on EPA's PD 2/3 Position

Dr. Vesselinovitch (CIEL Volume II, p.26) criticized the selection criterion for the pooled controls in the NCI Mouse Study. He stated that the selection criterion "is not scientific and tends to bias the controls in favor of a low background tumor incidence".

#### ii. EPA's PD 4 Position

Although the concern that the controls were not randomly chosen is a reasonable one, a review of the data on the pooled controls shows 1) no significant difference in hepatocellular carcinoma between the pooled controls and the matched controls, 2) comparable survival between all five groups that made up the pooled controls, and 3) comparable living and handling conditions, and comparable weight gains, among all of the controls. Furthermore, comparison of the low-dose lindane results with yet a larger, and different, pooled control group which NCI used for another chemical (endrin) also shows a significant response at the p = 0.05 level. Based on these considerations, EPA believes that the use of the pooled controls for analysis of the lindane data is both proper and justified (Memo, 1982a).

### c. Tumor classification

#### i. Comments on EPA's PD 2/3 Position

In his evaluation of the Tunstall lindane data (Thorpe and Walker, 1973), Dr. Vesselinovitch scores fewer tumors as hepatocellular carcinoma than do Thorpe and Walker. The tumors that Dr. Vesselinovitch does not call hepatocellular carcinomas are classified by him as either adenomatous nodules or adenomatoid (hyperplastic) nodules. He further argues that benign and malignant lesions should not be analyzed together, since he claims that they are different biological entities. (CIEL, Vol. II, pp. 37-38).

#### ii. EPA's PD 4 Position

EPA acknowledges that there are differences of opinion among pathologists as to the proper classification scheme for mouse liver tumors, particularly the benign nodular lesions. There are also differences regarding the categorization of specific mouse liver lesions. However, even with Dr. Vesselinovitch's evaluation scheme, there is a statistically significant incidence of combined hepatocellular carcinomas and adenomas, which is evidence for a tumorigenic response to lindane in mice. Furthermore, until there is evidence to the contrary, EPA assumes that hepatocellular adenomas and carcinomas are biologically related, and may represent different stages of a continuous biological process. Thus, it is appropriate to combine these incidences for risk assessment purposes (Memo, 1982a). NRDC (1983) endorses the Agency's position regarding tumor classification.

### d. IARC classification of lindane

#### i. Comments on EPA's PD 2/3 Position

Dr. Vesselinovitch (CIEL Vol. II, pages 73, 87, and Appendix F) states that the International Agency for Research on Cancer (IARC) classifies the available scientific data for lindane carcinogenicity as limited for animals and inadequate for humans, whereas he concluded that lindane is not carcinogenic in mice.

#### ii. EPA's PD 4 Position

Actually, IARC states that there is sufficient evidence for the carcinogenicity of lindane (gamma-HCH) in mice (IARC Vol. 20, page 223), limited evidence in animals, and inadequate evidence in man (Memo, 1982a).

### e. Alpha-fetoprotein levels in the Hanada study

#### i. Comments on EPA's PD 2/3 Position

In discussing the Hanada et al. study (1973) on lindane, Dr. Vesselinovitch (CIEL Volume II, page 42) states that the alpha-fetoprotein levels are only elevated in animals bearing true neoplastic lesions. Since these sera levels were not elevated in the mice that had nodular lesions (according to Hanada et al.), Dr. Vesselinovitch states that "none of the nodular lesions was true neoplasia", based upon the negative alpha-fetoprotein sera levels.

#### ii. EPA's PD 4 Position

The Hanada et al. (1973) study measured alpha-fetoprotein levels by the Ouchterlony method using antiserum obtained from the horse immunized with human alpha-fetoprotein. Becker and Sell (Cancer Research 34: 2489-2494, 1974) and Becker et al. (Cancer Research 35: 1510-1513, 1975) have actually shown that alpha-fetoprotein levels (measured by the rat alpha-fetoprotein radioimmunoassay technique) are immediately increased in rats after carcinogen exposure and before any pathologic alteration can be detected. In mice, Becker et al. (Cancer Research 37: 870-872, 1977) and Becker and Sell (Cancer Research 39:3491-3494,1979) reported elevation of serum alpha-fetoprotein levels observed in a majority of animals with liver tumors, using their mouse alpha-fetoprotein radioimmunoassay technique. Dr. S. Sell (telephone conversation with Dr. Haberman, CAG, Dec. 15, 1981) stated that the Ouchterlony method used in the Hanada et al. study was not very sensitive or reliable, when compared to the mouse alpha-fetoprotein radioimmunoassy using radiolabeled mouse alpha-fetoprotein. Therefore, even though the Hanada et al. study reported that the mice with liver tumors had negative alphae-fetoprotein levels, the Agency believes that the reported tumor results of this study show a carcinogenic response to lindane administration in these mice.

### f. Tumor classification in the Goto et al. (1973) study

#### i. Comments on EPA's PD 2/3 Position

Dr. Vesselinovitch (CIEL Vol. II, pages 37-38) stated that the tumors observed in the Goto et al. study are hyperplastic nodules consisting of normal-appearing cells, rather than hepatocellular tumors.

#### ii. EPA's PD 4 Position

The English translation of the German article states that "Hepatoma I - The tumor is a limited, small hyperplastic growth, grey-white, which has the appearance of a benign neoplasm (gutartiges Neoplasma) in the early stage.... The accumulated encapsulated cells press against the surrounding tissue, but they normally do not grow into the tissue". These authors continue to say that "Under the same experimental conditions, beta- and gamma-HCH also cause Hepatoma O-I (a benign liver tumor)." Therefore, Goto et al. (1973) are referring to a benign neoplasm causing local compression, i.e., by definition a hepatocellular adenoma, not a hyperplastic nodule, as Dr. Vesselinovitch states (Memo, 1982a).

### g. Possible cross-contamination in the NCI bioassay

### i. Comments on EPA's PD 2/3 Position

The submission from Paper Products (rebuttal #93) raises the possibility of cross-contamination by other carcinogens to the lindane-treated animals in the NCI bioassay, as an explanation of the high tumor incidence of the low-dose mice.

### ii. EPA's PD 4 Position

Although cross-contamination of the external environment in which these studies took place has been documented, there is no evidence suggesting contamination of the feed or cages (which were in any case protected by filter bonnets.) Furthermore, if cross-contamination had occurred, one would expect to see an increase in tumor incidence in the matched-control group, not just the low-dose test group. However, the carcinogenic response in the matched-control group is not significantly different from the historical-control group. Therefore, EPA does not consider that cross-contamination explains the differences in tumor response between treated and control groups (Memo, 1982a).

### h. EPA's PD 4 Final Position on the Presumption of Oncogenicity

The evidence that lindane is carcinogenic in mice is based on two lifetime studies, Thorpe and Walker, and the NCI study both of which show that oral administration of lindane causes hepatic tumors. Two subchronic studies in mice (Goto et al., Hanada et al.,) provide supportive evidence of oncogenicity consistent with that found in the two lifetime studies. Consistent with more recent risk assessment approaches, the CAG has used the multi-stage model for a revised slope of 0.03 $(ppm)^{-1}$ for the cancer risk estimates for PD 4. In addition to chronic bioassays of lindane itself, 2,4,6 trichlorophenol, a metabolite of lindane in rats and humans, was tested and found to be a carcinogen in laboratory animals. These tests will be discussed below. In addition, the following sections will address in vitro as well as in vivo metabolism, mutagenicity testing of lindane and the cancer bioassays. The genotoxicity issue for lindane and its importance for quantitative risk assessment will be considered in light of these related effects.

The NRDC (1983) is disturbed by reports "that the Agency views only two of the four studies as evidence of lindane's carcinogenicity." The preceding paragraph clearly indicates that the Agency believes lindane causes carcinogenic responses in mice. That position has not changed from PD 2/3. As stated, the position is based on two lifetime feeding studies with supportive evidence from two subchronic studies. None of the four studies has been "discounted" and all four are considered positive evidence of oncogenicity in mice. Moreover, a very conservative risk extrapolation model has been used to estimate the cancer risks.

### 3. Metabolism of Lindane

Extensive metabolism of lindane occurs mainly in the liver through dehydrogenation, dehydrochlorination, hydroxylation and oxidation. Many of the resulting metabolites appear as water soluble conjugates in the urine. Fitzloff, Portig and Stein (1982) studied metabolism of lindane by human and rat liver microsomes under aerobic conditions while Chadwick et al., (1981) have tabulated urinary metabolites of lindane from studies in rodents. Chadwick (1978) also studied the in vitro metabolism of lindane under anaerobic conditions. Metabolites include hexachlorocylohexene, pentachlorocyclohexene, tetrachlorophenol, trichlorophenol, pentachlorocyclohexenol and tetrachlorocyclohexenol.

However, as shown by these and other researchers, the total quantitative and qualitative profile of lindane metabolites is a function of species and experimental conditions (see also CAG, 1979). Therefore, any toxicity testing of lindane must take these variations into account. For example under anaerobic conditions, incubation of lindane with rat liver microsomes leads to two novel metabolites not found under aerobic conditions.

Certain metabolites of lindane are consistently identified no matter what the conditions or test species. One of particular interest is 2,4,6-trichlorophenol.

This metabolite, which is also observed in human urine (Starr and Clifford, 1972), has been found to be carcinogenic (see below).

In addition to membrane bound enzyme systems (microsomes), lindane may also be metabolized by cytosolic enzymes. In an in vitro study, Portig et al. (1979), concentrated on glutathione conjugate formation of lindane incubated in vitro. They found that conjugate formation of lindane occurred only in the presence of liver cytosol protein as a source of glutathione transferases, implying that conjugation is enzymatic in nature. Van Bladeren et al. (1981) has shown that other vicinal dihalogen compounds can be activated to mutagenic 2-halogenothioethers by conjugation with glutathione. Steric factors in the substrate can be important in determining whether the halogenothioether can be formed and whether it will be mutagenic. To date the role of glutathione and thioether formation in the mutagenicity of lindane has not been tested.

### 4. Mutagenicity

In the initial lindane RPAR, the Agency did not determine that the mutagenicity criterion has been exceeded. However, a review of mutagenicity studies on lindane is discussed here because of their bearing on the carcinogenicity issue. Lindane mutagenicity testing is summarized in Appendix IV.

Lindane has been tested for:

- gene mutations in microbial systems (Ames, yeasts, and Drosophila);
- chromosome aberrations in mammalian systems (in vitro and in vivo);
- other cellular end-points related to genotoxicity (DNA repair, and mitotic abnormalities in plant and mammalian cells); and
- mammalian cell transformation
- binding to DNA (C.I.E.L. sponsored, recently completed).

The composite of these studies reveals limited evidence for lindane's mutagenicity or genotoxicity (see Appendix IV). Except for two Salmonella studies by Rohrborn, gene mutation assays were negative in bacteria, yeasts, and Drosophila. Although there is a "suggestion" in some older studies for chromosomal effects (e.g., Tzoneva-Maneva, 1971, who reported slight increases in chromatid breakage and gaps), the majority of cytogenetic studies were reported as negative. Studies supposed to test for the integrity of cellular repair processes in bacterial and mammalian cells were also negative, as were cell transformation assays with human and hamster cell lines. Lindane has also been shown to have little or no genetic activity employing more sensitive tests for detecting DNA events. For example, negative results were reported in bacterial Ames testing in the presence of a microsomal metabolic activation system (S-9) from the tumor-susceptible mouse strain, CF-1. Negative results were also obtained in the presence of inactivators of potential nucleophilic reacting products, such as the epoxide hydrase inhibitor and glutathione depletor, 1,1,1-trichloropropene (TCPO), as well as following preincubation with nor-harman, a DNA intercalator and co-carcinogen, which is a known inhibitor of DNA synthesis and repair.

Some studies have reported spindle inhibition with lindane, but these have not been validated by EPA. That lindane may act as a spindle inhibitor is suggested by its cytological activity in plant cells, in which it produces c-mitosis and polyploidy, and in rat liver cells, where it increases mitotic indices and tetraploidy. However, other (non-validated) studies reported negative results (e.g., deBrabander 1976).

In the array of conventional mutagenicity assays already performed with lindane, however, a number appear to be missing (see Appendix IV). Chlorinated hydrocarbons present particular difficulties in short-term testing. Therefore, in addition to conventional testing with standardized hepatic microsomal fractions, adjustments in activation conditions would appear to be necessary for lindane.

In order to be considered valid, in vitro assays with lindane, would have to be performed under conditions as closely representative as possible of liver metabolism in vivo, e.g. presence/absence of oxygenation, time course of treatment, processing, etc. This is necessary because of metabolic considerations indicated in published studies with such organochlorines. For example, Sipes et al. (1977) conducted in vitro studies which indicate that the bioactivation of chloroform to species capable of binding to proteins, involves a cytochrome P450-dependent oxidation, and not a reduction, as found for carbon tetrachloride. Two separate groups, Mansuy et al. (1977) and Pohl et al. (1977) reported evidence that biotransformation of choroform to phosgene can occur. Both groups were able to trap, isolate, and identify a cysteine conjugate of phosgene that was produced when chloroform was incubated with microsomes in vitro. On the other hand, in vivo metabolic studies by Brown et al. (1974) have shown that $^{14}CHCl_3$ is rather extensively converted to $^{14}CO_2$. With the exception of recent work by Oesch (1980), none of the investigations listed in Appendix IV have addressed the necessary activation conditions as described above. Even the Oesch work failed to utilize the cytosolic fractions of liver preparations known to contain essential enzymes for the metabolic processing of xenobiotics, such as the sulfotransferases and dehydrogenases required to convert intermediates ("proximate" carcinogens) into their most highly reactive ("ultimate" carcinogens) forms which are not found in the customary microsomal fractions employed in testing.

NRDC (1983) questions why the Agency did not "validate" the studies that report spindle inhibition and why the Agency is "dismissing lindane's potential mutagenicity" in light of a number "conventional mutagenicity assays that appear to be missing." First, there are currently NO validated testing procedures specifically designed to assay directly for spindle inhibition (Mauer, 1983).

Thus, there is no standard method available by which to judge such studies. Second, the Office of Pesticides Programs has an agreement with CIEL to fulfill mutagenicity testing requirements under provisions of FIFRA, 40 CFR 158 (found in 47 FR 53192-53221 and 48 FR 2142-2147). The agreement was concluded on March 25, 1983. Mutagenicity was not one of the RPAR triggers. In spite of that, the Agency has not "dismissed" the subject of potential mutagenicity. It is seeking to extend its knowledge beyond the conventional battery of assays presently required for pesticide registration or reregistration (Mauer, 1983). Since there is currently limited evidence that would indicate the Agency should be concerned about mutagenicity, the data gaps need not be filled prior to completion of the RPAR. The information in the studies will aid in the understanding of mechanisms of oncogenesis.

Therefore, because of the data gaps in required testing, and insufficient consideration of exogenous activation in the tests performed, a conclusive evaluation of lindane's genotoxicity is not possible at this time. However, further testing will be done by the Centre International d'Etudes du Lindane, as explained in Chapter VII., F.

## 5. Bioassays of Lindane and its Metabolites in Laboratory Animals.

Although lindane has been tested extensively for carcinogenicity in laboratory animals, there are very few lifetime studies. Only two lifetime studies have been performed at the Maximum Tolerated Dose (MTD) in mice. Other mouse studies were of limited duration or dosages were low. Several rat studies have been performed, but with the exception of the NCI study in rats, these rat studies are severely limited on their utility as cancer bioassays by the small numbers of animals or short duration of testing. The most important mouse and rat studies are summarized below. For details on the data base examined by the Agency, the reader is referred to the CAG Risk Assessment on Lindane (1979).

Thorpe and Walker (1973) reported on the Tunstall Laboratory mouse study. In this lifetime study, 30 $CF_1$ mice of each sex were treated with a single oral dose, 400 ppm, of lindane (See Table 1 for details). A significant increase of liver tumors was found in the treated animals relative to the controls (96% in treated males and 95% of the females compared to 24% and 23%, respectively, in the controls). In addition, there was evidence of tumor metastases to the lungs in both sexes.

In 1977, the NCI published the results of a lifetime bioassay of lindane in $B_6C_3F_1$ mice. Test groups of 50 male and 50 female mice were fed lindane at 80 or 160 ppm. The incidence of hepatocellular carcinomas in low dose males (19/49) was significant when compared to pooled controls (5/49), but not in high dose animals.

Hanada et al. (1973) fed dd strain mice 100, 300 or 600 ppm lindane for 32 weeks. Sacrifice occurred at 37 or 38 weeks. Mortality in the treated groups was very high. However, malignant hepatomas were found in 3 out of 4 surviving males and 1 out of 3 surviving females in the high dose group compared with 0 out of 14 in the male controls and 0 out of 15 mortality and the short duration of the study, the high incidence of tumors noted above in 38 weeks of testing indicate that lindane may be carcinogenic in this strain of mice. This study, although flawed, supports the results of the other studies because it indicates that even a relatively short exposure to lindane may also induce tumors in mice.

In a 26-week study, Goto et al., (1972) fed ICR-JCL mice 300 and 600 ppm lindane. Five of ten surviving mice in the high dose group had liver tumors. Some of these tumors were classified as benign. Control group pathology was omitted. The CAG report notes that in Goto et al., as well as Hanada et al., liver lesions consisted of foci of altered cells with atypical appearance, consistent with the early stages of hepatocellular carcinoma. Although 50% of the high dose group developed tumors after a short period, it is difficult to definitively interpret the results because pathology in the controls was not reported. However, because of the young age of the animals and the short duration of the experiment, this study is consistent with the positive results seen in the other studies.

In the four studies described above, data are consistent in that males were more susceptible than females and the liver was the primary site of tumor development. In other mouse feeding studies, Ito et al., (1973) and Nagasaki (1972) gave lindane to male dd mice for 24 weeks. At high doses, there was liver hyperplasia, but in this short study, neither carcinomas nor hyperplastic nodules were found. Herbst et al. (1975) also performed two lifetime feeding studies in mice at low dose levels. No tumors were found.

In 1977, the National Cancer Institute published a bioassay for lindane in Osborne-Mendel rats. Fifty rats of each sex were fed lindane at 135 to 472 ppm for 80 weeks and subsequently observed for 29-30 weeks. The report concluded that no tumors occurred at a statistically significant incidence in the treated group of either sex.

As noted earlier, the remaining data base in rats is of limited utility because of short duration of testing or small numbers of animals tested. Summaries follow. Ito et al., (1975) fed male Wistar rats 500 ppm of lindane for 24 or 48 weeks. Survival was poor. Six treated rats were sacrificed at 24 weeks and 8 at 48 weeks. Slight hyperplasia was found at 48 weeks, but no neoplasia. Fitzhugh at al. (1950) fed groups of 10 female and 10 male Wistar rats 5 to 1600 ppm lindane for up to 107 weeks. Survival was poor. In 5-16 animals per dose group, toxic effects were observed in the liver down to 100 ppm, but no carcinogenicity was observed. Ortega et al., (1957) fed Sherman rats 50 and 100 ppm of lindane for up to 8 months. Serial sacrifices of one rat per sex per dosage group were performed at 2, 4 and 6 months. Three rats per sex per dose were sacrificed at 8 months. Liver toxicity was observed, but no evidence of carcinogenicity was found under the conditions of the study. Truhaut (1954) fed 10 male and 10 female rats per dose group, 25, 50 and 100 ppm lindane for their lifetimes. No oncogenicity was observed; however, slight liver hypertrophy was observed at 50 ppm and 100 ppm. No toxic effects were seen at 25 ppm.

In 1979, the NCI released a report on a bioassay of the lindane metabolite, 2,4,6-trichlorophenol in F344 rats and $B_6C_3F_1$ mice. The animals were fed the test chemical at 5,000 and 10,000 ppm. Halfway through the study, dosage for the mice was halved due to high mortality. Male rats showed a significant increase in leukemias or lymphomas. Females showed increased significance of hyperplasia of peripheral blood elements and bone marrow at both doses. Both male and female mice exhibited dose related increases in hepatocellular carcinomas or adenomas.

Table 1

Comparisons of Mouse Bioassays of Lindane

| ocol | NCI study, 1977 | Thorpe & Walker, 1973 | Goto et al., 1972 | Hanada et al., 1973 |
|---|---|---|---|---|
| n | $B_6C_3F_1$ | $CF_1$ | IRC-JCL | dd |
|  | 35 days | 4 weeks | 5 weeks | 6 weeks |
|  | both | both | male | both |
| Number/group | 50 | 30 | 20 | 10-11 |
| Dose (ppm) in diet | 80<br>160 | 400 | 600<br>300 | 100<br>300<br>600 |
| Duration | 80 weeks and 10-11 weeks of observation | 110 weeks | 26 weeks | 37-38 weeks |
| Results | Hepatocellular carcinoma in male mice at low-dose level of 80 ppm (19/49; P=0.001) High dose group not significant (9/46 vs. 5/49 P=0.16). | Liver tumors in males and females. 96% males and 95% females treated vs. 23-24% of controls (P less than 0.0001), 5-11% lung metastases. | Liver tumors in males (50% of treated males at 600 ppm; P=0.016) No tumors reported in controls. | Liver tumors in males and females (3 of 4 surviving males; 1 of 3 females at 600 ppm; No tumors in controls. Significant in males (P=0.005 at 600 ppm). |

## 6. Quantitative Risk Assessment of Lindane

In the Lindane Position Document 2/3, the Carcinogen Assessment Group estimated the carcinogenic potency of lindane as $b = 0.00732\ (ppm)^{-1}$ using the one-hit model. At low doses this model is a linear, non-threshold dose-response model. The Agency has considered the use of non-linear models for carcinogenic risk assessment of lindane. However, as noted above, only two positive studies have been reported in which the number of animals was sufficient for purposes of risk assessment. In one study (Thorpe and Walker), only one dose group was tested, and in the other (NCI), only one dose group showed a significant response. Under these circumstances, the data base is not significant for the use of any model but a linear one. In its rebuttal analysis, CAG describes in detail the reasons for using a linear model and its choice of the linearized multi-stage model for the Position Document 4 consistent with current risk assessment approaches.

The linear model gives plausible upper limits of risk. Using the linearized multi-stage model with a 95% upper confidence limit estimate and the further assumption that doses in mice and humans were equivalent on the basis of surface area (calculated as mg/kg b.w.) CAG estimates the linear slope factor as $q^* = 0.03\ (ppm)^{-1}$. The new slope estimate is 4.1 times larger than the old slope estimate because of two contributing factors as follows:

(a) 2.83 due to a different method of estimating human equivalent dose (surface area rather than dietary ppm).

(b) the remaining factor of 1.45 due to the use of an upper confidence limit approach in the current multistage exprapolation procedure, rather than a point estimate for slope used earlier.

## 7. Summary

The evidence that lindane is carcinogenic in mice is based on two lifetime studies, Thorpe and Walker, and the NCI study both of which show that oral administration of lindane causes hepatic tumors. Two subchronic studies in mice (Goto et al., Hanada et al.) provide supportive evidence of oncogenicity consistent with that found in the two lifetime studies. In three of these four studies, liver tumors were consistently found in males. In one, Thorpe and Walker, male and female mice exhibited liver tumors. Lung metastases were observed as well in the Thorpe and Walker Study. No evidence for oncogenicity of lindane has been found in rats. With the exception of the NCI lifetime bioassay, the other rat studies had severe limitations with respect to test duration and numbers of animals studied. However, 2,4,6-trichlorophenol, an animal and human metabolite of lindane, has been shown to cause lymphomas or leukemias in rats and hepatocellular carcinomas in male and female mice. To date, mutagenicity testing has been inconclusive and therefore the genotoxicity potential of lindane is indeterminate.

In conclusion, there is strong positive evidence that lindane causes hepatic tumors in mice. In addition, 2,4,6-trichlorophenol, a metabolite of lindane, has been found to be carcinogenic in both rats and mice. Until further, mutagenicity testing is performed, the genotoxicity of lindane can neither be confirmed or refuted. Because the biological data base for lindane is inadequate for a definitive choice of models, the linearized multistage model was used for PD 4 to provide a plausible upper limit risk estimate by extrapolating the risk linearly to low doses. In light of the carcinogenic effects of lindane in mice and the evidence of carcinogenicity of a metabolite of lindane in rats and mice, the Agency belives that lindane should be considered to have the potential for inducing carcinogenic effects in humans at some exposure level.

## B. The Presumption of Fetotoxicity/Reproductive Effects

### 1. EPA's PD 2/3 Position

EPA's presumption that lindane might cause reproductive and fetotoxic effects was originally based on three lindane feeding studies: Naishtein and Leibovich (1971), Petrescu et al. (1974), and Earl et al. (1973). At that time there were no studies available to the Agency in which technical lindane was dosed orally throughout the critical periods of organogenesis and in which the results were reported in sufficient detail for a critical review. In the PD 2/3, EPA concluded that the studies by Naishtein and Leibovich (1971) and Petrescu et al. (1974) had a number of flaws which rendered them inadequate to assess the reproductive effects of lindane. However, at that time, Earl et al. (1973) was still considered as unrebutted evidence of lindane's fetotoxic effects. In addition, several studies came to the Agency's attention during the re[illegible] [illegible] which influenced its decisions concerning fetotoxicity. A dis[illegible] [illegible]ese considerations is in PD 2/3 (EPA, 1980a, pp. II-6 to II-16).

EPA was unable to use the Earl study to determine a no observed effect level (NOEL) and therefore did not use it to calculate margins of safety (MOS) for fetotoxic effects. The Agency did not use it because both doses (15 and 7.5 mg/kg/day) were thought to cause adverse effects. The Agency did, however, use it in a qualitative sense in that the Earl et al. study influenced its decision to set the maternal and fetotoxic NOEL at a level below 7.5 mg/kg/day i.e., 5 mg/kg/day, based on the three pivotal oral teratogenicity studies in rats (Palmer and Lovell, 1971), rabbits (Palmer and Neuff, 1971), and mice (Bauer and Frohberg, 1972 a and b).

### 2. Comments on EPA's PD 2/3 Position

Comments submitted in response to PD 2/3 focused on two contentions: 1) lindane does not produce "selective" fetotoxic effects, because the effects occur in laboratory animals only at or above doses which cause maternal toxicity, and 2) the actual NOEL for fetal effects is four to six times higher than that used by the Agency in PD 2/3. Comments also stated that exposure estimates used by the Agency were unrealistically high, and that if more realistic estimates had been used, it would be clear that the margins of safety were ample (CIEL Volume I, pages 42-54.)

NRDC (1983) contends that the Agency changed its analysis of lindane's reproductive and fetotoxic effects from PD 2/3 to PD 4. NRDC asserts that several oncogenicity studies on lindane showed findings of testicular atrophy. NRDC stated that the EPA refused to rely on the study by Earl et al. (1973) and that EPA mischaracterized the results reported by Khera et al. (1979). Finally, NRDC is concerned with EPA's draft PD 4 position that lindane causes fetal effects in test animals only at or above doses which cause maternal toxicity.

At the SAP meetings of July 24 and August 13-14, 1980 (which followed issuance of PD 2/3), questions were raised about whether lindane affects the adrenals, pituitary, and gonads, as they relate to reproductive or fetotoxic effects. A question was also raised about the correlation between reproductive effects and adrenal ascorbic acid depletion.

### 3. EPA's PD 4 Determination

In response to these concerns, EPA conducted a thorough reevaluation of the thirteen studies on the potential reproductive and fetal effects of lindane (EPA, 1982a.) These studies are summarized in Table 1. Based on its reevaluation of these data, EPA revises its position on the presumption of fetotoxicity and reproductive effects as follows (EPA, 1982a; Memo, 1982b; Memo, 1982e; Memo, 1982g):

a. The Agency's concern that lindane might cause adverse reproductive effects, as distinguished from fetal effects, has been successfully rebutted. This conclusion is based on the fact that testicular [illegible] in the NCI report (NCI, 1977) did not appear to be related to the treatment of the rats. The NCI report noted that statistical comparisons of treated with matched and pooled controls showed no significant differences for this effect. Further, there were no treatment related reductions in pregnancy rate or litter size in the multigeneration reproduction study in rats (Palmer et al., 1971).

b. After a thorough reevaluation of the Earl et al. (1973) study, the Agency only used the study to a limited extent in the assessment of fetotoxic effects. There is no indication in the study whether "average pups/litter" includes live pups only or both live and stillborn pups. In order to support a conclusion regarding the toxicological significance of the rise in percentages of stillborn pups, live pups per litter should be presented. The 7.5 mg/kg group (stillborn rate = 22.7%) and the 15 mg/kg group (stillborn rate = 17.9%) were close to the upper range of variation in untreated dogs (19%) at the laboratory conducting the study and, therefore, there is no dose response. The results reported do not suggest that lindane has no potential to cause fetotoxicity, but the circumstances described here indicate that the results are equivocal. Thus, the Agency has not rejected the results of Earl et al. but considers the study of limited utility. Further, the fetotoxicity of lindane has been sufficiently studied in several other properly controlled studies, which allows a definitive scientific conclusion.

The Earl et al. report did not contain a description of maternal effects, and in view of results from other animal studies (Palmer and Lovell, 1971; Palmer and Neuff, 1971; Reno, 1976 a and b; and Bauer and Frohberg, 1972 a and b), data on maternal toxicity are necessary in the assessment of the results.

c. The results reported by Khera et al. (1979) do not indicate fetotoxic effects below a dose level reported to cause slight maternal toxicity. As stated in PD 2/3, the increased number of fetuses with anomalies in the mid-dose group is unlikely to be compound related. Since there was no concomittant increase in the number of litters with anomalous fetuses in that group and no increased incidence of fetuses with anomalies was noted in the highest dose tested. Results reported by Palmer and Lovell (1971) showed that anomalies similar to those reported by Khera et al. (1979) were observed at maternally toxic doses, and in view of the lack of increased effects in the highest dose tested by Khera et al., the increased incidence of affected fetuses is more likely to be a coincidental result. Because of these factors, the study was not used to set a NOEL.

d. The eight studies submitted in rebuttal to the Agency's PD 1 and PD 2/3 followed conventional protocols and were reported in greater detail than the three studies originally used by the Agency to support the presumption of fetotoxicity. In PD 2/3 the Agency rejected the rebuttal attempt and noted that fetotoxic effects were observed in the submitted studies at or near (both below and above) doses that caused maternal toxic effects. In PD 2/3 the Agency also selected certain studies (Palmer and Lovell, 1971; Palmer and Neuff, 1971; Bauer and Frohberg, 1972; Khera et al., 1979) for determining a NOEL of 5 mg/kg/day.

For this PD 4, the Agency reevaluated the eight rebuttal studies and the five other studies discussed in PD 2/3. The Agency concluded that several of these studies are adequate to confirm that fetal effects occur only at or above doses that also cause maternal toxicity. Fetal effects are not expected below maternal toxicity levels because the one instance in which this may have occured is believed to have been coincidental (see discussion of Khera et al. above). The Agency also reconfirmed the NOEL of 5 mg/kg/day based on the same studies cited above in PD 2/3, except for Khera et al. (due to its limitations discussed above). The value of 5 mg/kg/day as a NOEL is consistent with other toxicity data based on subchronic dosing of lindane. From these same four studies (Palmer and Lovell, 1971; Palmer and Neuff, 1971; Bauer and Frohberg, 1972 a and b), the NOEL for fetal effects (in the presence of maternal toxic effects) is 10 mg/kg/day.

e. CIEL submitted to EPA a thorough response to the Scientific Advisory Panel's concern that lindane might affect the reproductive glands. Their conclusions, with which EPA agrees, are that:

- Multi-generation, chronic and subchronic studies in the rat and in dogs have failed to show any effects on adrenal, testicular, or ovary weights (absolute, as well as relative, weights). No findings have indicated effects on adrenals or gonads which could be related to reproductive or fetotoxic effects.

- Higher urinary excretion of Vitamin C was observed in the studies by Trivonva et al. (1970), Petrescu et al. (1974), and Naishtein and Leibovich (1971). This is a frequent side effect of enzyme induction in rodents. There was no evidence of a reduction of ascorbic acid, but there was evidence of increased synthesis of ascorbic acid in the liver of test rats.

In conclusion: EPA's reevaluation finds that lindane (a) does not cause reproductive effects, but (b) does cause adverse fetal effects in test animals, but only at or above doses which also cause general toxic effects in the mother. It is not possible to determine whether these effects are "selective" (direct) fetotoxic effects, or whether they are indirect effects which are caused by the effects on maternal animals. Nonetheless, the Agency has a responsibility to protect fetuses from possible adverse effects of lindane, whether these effects arise from selective and direct activity on the fetus, or whether they arise indirectly through toxic effects on the mother. From a regulatory and practical standpoint, the data indicate that protecting mothers from acute toxic effects will simultaneously protect fetuses from possible adverse effects. Therefore, the regulatory decision for fetal effects is based on both the NOEL for maternal toxicity and the NOEL for fetotoxicity. The data indicate that this will be adequate to ensure that neither general nor fetal toxicity (direct or indirect) will occur (EPA, 1982a; Memo, 1982b; Memo, 1982e; Memo, 1982g).

This NOEL (5 mg/kg/day) is the same dose level used in the PD 2/3 as a NOEL for fetotoxicity. The only difference between this PD 4 position and the PD 2/3 position on this issue, is that by referring to this dose level as a NOEL for general toxic effects, the Agency is acknowled[illegible] there is no persuasive evidence for a selective effect on fetuses [illegible] do not produce general toxicity. The NOEL for fetotoxicity is apparently 10 mg/kg, but this has little regulatory significance, since the 5 mg/kg general toxicity NOEL would be applied to all use situations for which the fetotoxicity NOEL would be appropriate.

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## TABLE 2

### COMPARISON OF NO OBSERVED EFFECT LEVELS FOR MATERNAL AND FETAL EFFECTS

| Species | Route of Administration | NOEL for Maternal Effects | NOEL for Fetal Effects | Ratio Fetal NOEL to Maternal NOEL | References |
|---|---|---|---|---|---|
| Mouse | Oral (gavage) | 30 mg/kg/day | 30 mg/kg/day | 1 | Bauer and Frohberg, 1972a and 1972b |
| Pig | Dietary | >20 mg/kg/day | >20 mg/kg/day | ** | Duee et al., 1975 |
| Dog | Dietary | * | * | * | Earl et al., 1973 *** |
| Rat | Oral (gavage) | * | * | * | Khera et al., 1979 *** |
| Rat | Oral (gavage) | * | * | * | Naishtein and Leibovich, 1971 *** |
| Rat | Oral (gavage) | 5 mg/kg/day | 10 mg/kg/day | 2 | Palmer and Lovell, 1971 |
| Rabbit | Oral (gavage) | 5 mg/kg/day | 10 mg/kg/day | 2 | Palmer and Neuff, 1971 |
| Rat | Dietary | >5 mg/kg/day | >5 mg/kg/day | ** | Palmer et al., 1972 |
| Rat | Dietary | * | * | * | Petrescu et al., 1974*** |
| Rat | Subcutaneous | 15 mg/kg/day | >30 mg/kg/day | >2 | Reno, 1976a |
| Rabbit | Subcutaneous | 5 mg/kg/day | 5 mg/kg/day | 1 | Reno, 1976b |
| Rat | ** | * | * | * | Trivonva et al., 1970 *** |

*Not determinable because of insufficient information to evaluate study.

**Not determinable because dosages were not high enough to cause fetal or maternal toxicity.

*** Of limited or no regulatory significance.

# III. OTHER POSSIBLE ADVERSE EFFECTS

## A. EPA's Concern Regarding Acute & Subacute Hazards to Humans and Domestic Animals

### 1. EPA's PD 2/3 Position

The Agency based its original concern regarding the acute effects of lindane on numerous studies in humans and animals which show that lindane causes symptoms of acute and subacute toxicity typical of central nervous system (CNS) stimulation (PD 2/3, pp. II-22 to II-31, and pp. II-77 to II-79.)

In PD 2/3, EPA determined an approximate no-effect level (NOEL) of 2.5 mg/kg/day, based on Hayes (1963), and supported by the results of Desi (1974). The following points were emphasized:

- effects at low dosage levels may be reversible;
- subtle, sub-symptomatic effects may occur below 2.5 mg/kg/day, and these changes could affect the functional efficiency of nerve transmission;
- among adults there may be a high degree of variation in sensitivity to the CNS effects of lindane; and
- sensitivity in the young may be considerably greater than that of adults

Risk to humans was evaluated by comparing the 2.5 mg/kg/day NOEL with the highest estimated daily exposure for each use of lindane. The resultant margins of safety (MOS) for adults may be found in the PD 2/3 (pages II-74 and II-75.) There was not enough information to calculate separate margins of safety for children, but they are assumed to be lower than those estimated for adults.

Studies illustrating the types of effects lindane may cause at various doses are summarized below (EPA, 1982a):

- At low-doses, lindane produces apparently reversible toxicological effects. At 3 mg/kg/day, lindane taken orally caused temporary dizziness in humans (Hayes, 1963). Similarly low doses (2.5 mg/kg/day given for 22 to 40 days) were reported to cause decreased learning ability and affected operant behavior in rats (Desi, 1974). (Note that, for the reasons cited below, the Desi and Hayes studies have not been independently relied upon for estimating a NOEL in the PD 4.) Decreased food consumption was observed at 5 mg/kg/day in Palmer and Neuff, 1971; at 5 mg/kg/day in Reno, 1976b; at 10 mg/kg/day in Palmer and Lovell, 1971; and at 30 mg/kg/day in Reno, 1976a. Body weight loss was observed at 5 mg/kg/day in Palmer and Neuff, 1971; and at 10 mg/kg/day in Palmer and Lovell, 1971.

- Medium-dose studies showed more serious, possibly non-reversible effects such as nerve impairment. Schwarz and Kuschowitz (1968) showed that lindane slowed the process of excitation in in vivo experiments on the retina of frogs. These results are consistent with the in vitro results in rat nerve tissue (White and Larrabee, 1973), which showed that lindane inhibits transmission of nerve impulses at synapses in ganglia. Dellamagne et al. (1950) also reported synaptic nerve damage in dogs given repeated intraperitoneal injections of 10 to 30 mg/kg for up to 44 days.

At high doses, lindane is capable of inducing convulsions and death. Hanig et al. (1976) produced convulsions with doses of 60 to 120 mg lindane per kg body weight, applied to rabbits' skin following shaving, depilation, and stripping. The same effects were seen when doses of 2.4 to 11.5 mg/kg, via the carotid artery, were given to dogs, cockerels, and rats (Litterst and Miller, 1975; St. Omer, 1971).

## 2. Comments on EPA's PD 2/3 Position, & the Agency's PD 4 Determination

### a. Basis for calculating the NOEL

#### i. EPA's PD 2/3 Position

CIEL contended that the Hayes (1963) data should not have been used by the Agency to calculate an acute effects MOS, because they are based upon subacute rather than acute exposure to lindane. The human studies referred to in PD 2/3 (Hayes et al., 1963) were considered by rebutters to lack specific information necessary for interpretation of reported observations. According to commentors, these deficiencies included, no references of sources for the data presented, no information on body weights or health status of the "patients" receiving lindane, no information about the size of the test groups and no inclusion of a placebo dosed or untreated group. Rebutters also contended that comparisons of single with split dosage regimens is inappropriate and further, that inadequate reporting of details rendered the human data useless for purposes of establishing a no-observed effect level. CIEL also stated that thirty years of clinical use of lindane suggest that the NOEL is considerably higher than 2.5 mg/kg/day, although CIEL did not attempt to derive a NOEL from the clinical data available (CIEL Volume I, pages 54-55). NRDC (1983) objects to the general toxicity NOEL of 5 mg/kg/day because "no standard toxicicological studies exist" and because a 32-week study on beagle dogs indicated toxic effects at 5 mg/kg/day.

#### ii. EPA's PD 4 Response

The Agency and commentors agree that lindane causes acute effects. Upon review of the data reported by Hayes et al. (1963), the Agency acknowledges the deficiencies noted by commentors. Although the deficiencies preclude use of the study results for calculating margins of safety, the Hayes et al. data support the Agency's previous conclusion (in PD 2/3) that humans and animals, with similar lindane exposures are likely to exhibit similar signs of toxicity.

In view of considerations described in section III.1.b.iii. below, and results of studies described in section II above, a NOEL of 5 mg/kg/day can be established for lindane toxicity.

In its comment about documentation to support the statements about human experience with lindane, the NRDC did not discuss the citations on page 20 of the February draft PD-4. Citations by the Agency included reports by Kramer et al. (1980), Morgan et al. (1980), Ginsberg et al. (1977), Halpern et al. (1950), and Woolridge (1948). These references support the conclusion that a 5 mg/kg NOEL is likely to be appropriate in assessing the acute hazards of lindane.

The 32-week dog study mentioned by the NRDC, characterized potential hazards that are more likely to be associated with longer exposure periods. The teratogenicity studies are more comparable to shorter exposures, and thus they are more appropriate to an assessment of potential acute hazards.

### iii. EPA's PD 4 Position

The studies reviewed by the Agency for establishing a NOEL for lindane with respect to the CNS stimulation effects are consistent with Hayes (1963) and Desi (1974), although neither of these two studies is sufficient to independently establish a NOEL (as explained above).

The no effect level for general toxicity found in the reproductive studies was 5 mg/kg/day. Reversible CNS effects have also been noted in Hayes (1963), Desi (1974), and Joy et al. (1982) at 3, 2.5, and less than 5 mg/kg/day, respectively. Since many of the studies investigating lindane's neurological effects are specific in nature (e.g., Joy et al., 1982; Desi, 1974), they are more likely to establish lower no-effect levels than the more generalized, conventional subchronic toxicity tests. Such no-effect levels are of questionable toxicological significance because of the specific and reversible nature of the effects and the studies were not designed to determine the toxicological significance of such effects.

Clinical evidence from lindane's human pharmaceutical uses suggests that exposures somewhat higher than 5 mg/kg/day do not usually result in acute neurotoxic symptoms (Kramer et al., 1980; Morgan et al., 1980; Ginsberg et al., 1977; Halpern et al., 1950; Woolridge, 1948). Also, the literature on lindane suggest that 1.25 mg/kg/day is the approximate NOEL for liver enlargement, when exposure is chronic (Memo, 1982c). These factors as well as those described in section b., below, led the Agency to conclude that 5 mg/kg/day is an appropriate no-effect level for the reversible C[illegible]

## b. The Nature of Effects On the Nervous System

### i. EPA's PD 2/3 Position

The Agency described the toxic effects associated with a range of dosage levels (see section A. 1., above). In addition, the Agency cited data (Koransky and Ullberg, 1964) which indicated that lindane accumulates in the white matter of the brain of laboratory rats. This observation was used by the Agency to support the conclusion that lindane adversely effects the central nervous system (CNS).

### ii. Comments on EPA's PD 2/3 Position

CIEL contested EPA's statement in the PD 2/3 that lindane has an affinity for white nerve tissue, "where it accumulates and causes symptoms of acute and subacute poisoning...." They pointed out that in PD 2/3, EPA incorrectly reported that the Koransky and Ullberg (1964) study found the gamma isomer of hexachlorocyclohexane (lindane) to accumulate exclusively in the brain structures containing white matter. In addition, rebutters stated that there is no evidence to suggest that lindane causes delayed adverse effects on the nervous system (CIEL Volume I, pp 56-59).

The effects characterized by existing data suggest early warning signs of toxicity according to rebutters. Rebutters contended that many of the studies do not characterize the toxicological significance of the specific effects observed. One study involved in vitro investigations (White and Larabee, 1973) while others (Dellamagne, 1950; St. Omer, 1971; Litterst and Miller, 1975; and Koransky and Ullberg, 1964) used methods of administration (via injection or infusion into the carotid artery) which are not relevant to routes of human exposure. Two experiments (Hanig et al., 1976; and Schwartz and Kaschowitz, 1968) did not establish no-effect levels. The studies of lindane's effects on behavior in rats (Desi, 1974) were described by rebutters as inconsistent and not dose-related.

### iii. The Agency's PD 4 Response

EPA acknowledges that it incorrectly reported the results of the Koransky and Ullberg (1964) study. The study reported results for the alpha but not the gamma (lindane) isomer of hexachlorocyclohexane. The alpha isomer, which is known to have approximately the same lipophilicity as lindane, was reported to accumulate exclusively in brain structures containing [illegible] matter. However, these findings were not reported in det [illegible] cannot be evaluated for its accuracy.

Somewhat different results were obtained in the dog by Litterst and Miller (1975), who analyzed twelve regions of the brain for lindane concentrations. All regions sampled had approximately equal concentrations of lindane in spite of different proportions of white to grey matter.

As noted above, many of the studies used inappropriate routes of administration. They investigate specific neurological effects without determining the toxicological significance of the observed effects.

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These deficiencies limit the value of these studies for purposes of establishing a no-effect level.

The Agency re-evaluated the studies reported by Desi (1975) and agrees that there are inconsistencies in the report. However, the results suggest that lindane affects neuromotor function (Reiter, 1982) which is consistent with in vitro studies in rats (White and Larabee, 1973) and the study on the frog retina (Schwartz and Kaschowitz, 1968).

Due to inconsistencies such as inappropriate statistical analyses, the possibility exists that variables other than lindane may have affected results, and the apparent reversibility of lindane's effect on behavior of test animals (Reiter, 1982), the Desi study cannot be used to demonstrate no-effect levels for general neurological effects (see discussion below).

Subsequent to the publication of PD 2/3, a study by Joy et al. (1982) came to the Agency's attention. The study showed that 3 and 10 mg/kg/day doses (administered by gavage for 5 consecutive days in rats) increased the reactivity of the brain of rats to electrical stimuli (kindling). There were no effects on behavior noted by the authors. One mg/kg/day had no apparent effect.

Since the electrical stimuli were administered through electrodes implanted in the brains of the rats, the study does not characterize the toxicological significance of lindane's effects (Zendzian, 1982).

As indicated by rebutters and in the preceding discussion, the animal studies evaluated specific aspects of lindane's neurological effects over a wide range of doses. Due to the specific nature of these studies, a no-effect level derived from them is likely to be lower than that found in standard, less specific, toxicological studies normally used to evaluate a chemical. The lowest no-effect level of 1 mg/kg/day suggested by results from Joy et al. (1982), is less than the 5 mg/kg/day NOEL found in the reproduction and teratology studies listed in Table 1. In light of the difficulties described earlier regarding the studies by Desi (1975) and Joy et al. (1982), the studies are useful only as supportive evidence for determination of a no-effect level.

As noted by rebutters, the effects described by Desi (1975) are apparently reversible (Reiter, 1982). Joy et al. (1982) cited other studies that suggest the need for additional experiments to determine whether the CNS effects they observed are reversible (Zendzian, 1982). Based on these considerations, the Agency agrees that the neurological signs observed at low doses can best be interpreted as warning signs of lindane intoxication.

NRDC (1983) objected to the Agency's determination of the 5.0 mg/kg/day NOEL for general toxicity. NRDC was also concerned about the "lack of standard toxicological data." Finally, NRDC asserted that the 5.0 mg/kg/day NOEL "will justify higher exposures to children." As discussed above, the 5.0 mg/kg/day NOEL was based on studies where irreversible effects were observed. Studies where reversible effects were observed were not considered sufficient for establishing a NOEL. The Agency does not believe that there is a lack of toxicological data with which to establish a NOEL. Regardless of these technical issues, it should be noted that the acute effects observed in the available studies have not and do not meet an RPAR criterion, and further analysis is not necessary.

### c. Sensitivity of Children to Lindane

#### i. Comments on EPA's PD 2/3 Position

Rebutters disputed the Agency's concern that children are more sensitive to the toxic effects of lindane than adults, stating that "the Agency failed to consider that enhanced sensitivity of children is a problem common to all chemicals." Furthermore, they stated that the high incidence of lindane poisonings resulted from accidental misuse, such as ingestion by children, rather than from special sensitivity of children to lindane's effects. However, the Scientific Advisory Panel's review stated that "The Panel agrees with EPA that lindane is substantially more toxic to young than adults in both humans and domestic animals..."

### ii. EPA's PD 4 Response

Because of these different interpretations of the data, EPA carefully reevaluated the issue of special child sensitivity (EPA, 1982a, pp. 29-30, 32-37, and 46-47; EPA, 1983a). The results are as follows:

Equivalent dosages (on a surface area basis) of lindane, applied to adults and children, produce a greater mg/kg body weight dose in children. This is consistent with the fact that children have a higher ratio of surface area to body weight than do adults. Other factors which theoretically enhance toxicity to children of many chemicals are greater skin permeability in children, and the lack of mature hepatic conjugating enzymes for detoxification and excretion. The best animal study to date (Solomon et al., 1971) does not suggest differences between newborns and adults with respect to lindane absorption. The doses used were relatively low (0.5-2 mg/kg) and in a range that is not associated with definitive toxic effects (see Section III. A. 2. above). Therefore, the study cannot be used to rule out the possibility of differences in sensitivity.

The other animal studies reviewed have flaws which make them less useful for evaluating childhood sensitivity. In Hanig et al. (1976), the results may have been compromised by the fact that the animals were subjected to severe treatment of their skin (EPA, 1982a). Furthermore, the results are of questionable reliability because of the very small test groups used, the lack of a vehicle control, and the lack of differentiation between the surface-to-body-weight ratio in weanlings compared to adults. However, qualitative effects were noted in weanlings which were absent in the adult animals. In Mohrmann and Weisberger (1977), the doses were lower than those used in the Hanig study, and no effects were seen, so comparison of the younger to the older groups is not appropriate.

The Agency has also carefully reviewed the clinical reports of lindane intoxication, many of which involved children. There were significant differences in the clinical observational procedures, differences in integrity of the skin surfaces of the patients, and differences in the conditions of exposure. These variations preclude the use of such case reports in any quantitative way, but support the Agency's concern that children may be more susceptible to toxic effects from exposure to lindane. However, none of these data show a distinctive and peculiar response by different age groups, other than the generally established sensitivity of the young to intoxication, as discussed above. Special warnings concerning exposure of children, and child resistant packaging where appropriate, are imposed on lindane products. The Agency also notes that with these use precautions, exposure of children to lindane is likely to be far less from pesticidal use than from the pharmaceutical use for treatment of lice and mites. The pharmaceutical use is regulated by the Food and Drug Administration under the Federal Food, Drug, and Cosmetic Act.

## B. Possible Association Between Lindane and Blood Dyscrasias

### 1. EPA's PD 2/3 Position

In PD 2/3, EPA stated that available data on lindane were not sufficient to establish a cause-effect relationship between lindane and blood dyscrasias. However, the Agency noted that two epidemiologic studies were in progress at the time of publication of the PD 2/3: one in Iowa, and the other in Hawaii (PD 2/3, pages II-21 and II-22.)

### 2. Comments on EPA's PD 2/3 Position

The FIFRA Scientific Advisory Panel, in its comments on the Agency's PD 2/3 position, stated: "The Panel agrees with EPA that... chronic exposure can sometimes result in disastrous blood dyscrasias." However, this was a misstatement of the Agency's actual position, which was, and still is, that there is not sufficient information to establish a cause-effect relationship between lindane and blood dyscrasias.

NRDC (1983) urges "the Agency to consider the results of the Hawaiian epidemiological study currently underway regarding this hazard...." The Agency has done so, and in discussion under III.B.3., below, has found no evidence to alter the original PD 2/3 conclusion.

### 3. EPA's PD 4 Position

The Iowa study (Morgan, 1980) surveyed 215 households in Iowa and Illinois where lindane vaporizers were used. This population was chosen because vaporizer use resulted in continuous, high levels of exposure. The stated intent was to discover symptoms which would suggest lindane-related injury.

The investigators reported no correlation between lindane blood levels and the occurrence of adverse hematologic effects. Blood levels of lindane did correlate significantly with age, and so did several hematology and biochemical measurements, but it was not known whether these resulted from an actual lindane-related effect, or from confounding environmental factors or methodological variations. The most important result was that no obvious cases of anemia or blood dyscrasias were found in any of the individuals routinely exposed to lindane.

The Agency has received the first draft of the Hawaii study. The purpose of the study has been to collect case histories of people with blood dyscrasias in Hawaii and to attempt to correlate these with past exposures to pesticides. Out of 96 case histories of individuals with various blood dyscrasias (including aplastic anemia), only 2 reported any contact with lindane. No statistically significant association of exposure to lindane with the incidence of blood dyscrasias was seen.

One other study (Kramer et al., 1980) in humans, does not establish a cause-effect relationship between lindane and blood dyscrasias because the lack of follow-up and complete medical histories prevents interpretation of the results (EPA, 1982a).

In conclusion, the Agency received no new data that would alter the previous position. The Iowa epidemiology study discussed above similarly provides no information to establish a cause-effect relationship between lindane and blood dyscrasias.

### C. Acute Toxicity to Aquatic Wildlife

#### 1. EPA's PD 2/3 Position

The Agency's original presumption of acute toxicity to aquatic organisms was withdrawn in the PD 2/3, because no lindane products were registered for aquatic uses. However, the Agency stated concern about the possibilities of drift or runoff should any non-aquatic lindane product be misused, since lindane is "very highly toxic" to aquatic wildlife (its $LC_{50}$ is less than 0.1 ppm; see Henderson et al., 1959; Eisler, 1970).

#### 2. Comments Received, and EPA's PD-4 Final Position

The Agency received two comments on this issue. One was a series of letters (3000/10c, #104-109) expressing concern that lindane was killing the insect populations of the White Clay River (in Pennsylvania and Delaware), thereby adversely affecting fish populations in the river. Several possible sources of the lindane contamination were cited, but there was no evidence with which to determine the exact source or sources. However, the Agency has since received reports from the two affected states, which have been monitoring lindane levels in the water since September, 1978. Of 27 readings, all but four have been below one-tenth the acute LC 50 value (.2 parts per billion for the most sensitive species, the brown trout.) The four values which exceeded one-tenth the acute LC 50 value occurred between September and December 1978, and have never occurred since. In addition, readings on fish residues have been consistently low (Memo, 1982h.)

The U.S. Department of Agriculture advised EPA that aerial spraying of lindane for forestry use would be unadvisable due to the possibility of runoff and drift (see Appendix I).

Since lindane is very highly toxic to aquatic organisms, but is not registered for direct aquatic application, EPA is chiefly concerned about avoiding misuse and/or application practices which could result in drift or runoff. Therefore, although the PD 2/3 withdrew the presumption of acute toxicity to aquatic organisms, the Agency has taken this issue into account in its risk-benefit analysis, and will require label prohibitions against practices which could result in significant amounts of drift or runoff, such as improper disposal of dips, and aerial application.

### D. Possible Population Reductions in Non-target Avian Species

No new evidence was submitted to the Agency since the PD-2/3. The Agency maintains its position that there are insufficient data to initiate a rebuttable presumption on the basis of population reductions in non-target avian species.

### E. Possible Isomerization

In the PD 2/3, EPA concluded that isomerization of lindane had not been established; this was a concern because other isomers of BHC are oncogenic in mice.

A 56-day feeding study in rats was submitted to the Agency since issuance of the PD 2/3, showing that no significant isomerization of lindane to the carcinogenic alpha or beta isomers of BHC occurs in rats above the limit of detection (Burkoth and Paul, 1981; confidential rebuttal #94-D). The study used an appropriate protocol, sufficient numbers of control and treated male and female rats, and appropriate (maximal) doses administered orally (gavage). The study was capable of detecting very low percentages of isomerization, but no indication of significant isomerization to the alpha or beta isomers of BHC was found.

Two limitations of the data are that the study was not long enough to detect possible long-term bioaccumulation of isomers, and that isomerization in rats has only limited relevance to the situation in mice, the only species in which carcinogenic effects have been observed. However, these limitations are minor and do not change EPA's position that isomerization of lindane has not been established (Memo, 1982a).

### F. General Toxicity of Lindane

The toxicity of lindane has been the subject of many studies. Liver toxicity, resulting in increased liver weight and hepatic lesions, is characteristic of lindane. The acceptable daily intake for lindane was set from a NOEL of 1.6 mg/kg/day from a 2 year chronic feeding study in dogs (WHO, 1974). In a 2 year feeding study in rats, levels at and above 2.5 mg/kg/day produced liver weight increases and hypertrophy. The NOEL in this study was 25 ppm or 1.25 mg/kg/day (Truhaut, 1954; CAG, 1979).

A recently submitted 3 month, subchronic oral feeding study in rats has been cursorily reviewed by the Agency (Locke, 6/17/83). The NOEL was 4 ppm or approximately 0.3 mg/kg/day. At the next highest dose (20 ppm in the diet), kidney damage, which was not reversible after a 6 week recovery period, was evident in both males and females.

Based on the results of this study, the Agency will give high priority to the development of a Registration Standard for lindane. In order not to delay the implementation of the regulatory measures resulting from the RPAR review of lindane, it was decided to issue this PD 4 at this time. As part of the Registration Standard review, the Agency will perform a thorough evaluation of lindane's general toxic effects, including a review of the complete chronic and sub chronic data base.

# IV. EXPOSURE

## A. Non-dietary exposure to lindane

Detailed discussions of many lindane uses are provided in the exposure analysis narrative, contained in Appendix III. In overview, differences between the PD 2/3 and PD 4 exposure estimates are due to the following:

1. In PD 4, EPA uses exposure information and studies which were not available when the PD 2/3 was published. Comments received on the PD 2/3 exposure analysis were generally of excellent quality, and provide the Agency with better, more detailed information which enables a more informed regulatory decision. The Agency also uses recently published studies on similar chemicals, where they provide better surrogate data for making exposure assumptions. For example, the Agency uses a more appropriate study for estimating exposure to applicators who use back-pack sprayers (Appendix III.)

2. In PD 4, EPA considers commonly accepted use practices, rather than the theoretical worst-case use practices as were assumed in PD 2/3, because better data are available to replace the previous theoretical assumptions. Ranges of estimates are presented for those uses where there was enough information to do so.

3. In PD 4, EPA acknowledges those uses in which protective clothing is already routinely worn therefore eliminating risk assessment when protective clothing is [illegible]. This information helped the Agency to determine that the protective clothing requirements under consideration will not require changes in those use practices. It also assured the agency that imposing protective clothing requirements for other uses will be effective in reducing risks.

Assumptions regarding the rate at which lindane is dermally absorbed are the same in PD 4 as in PD 2/3. Liquids are assumed to be absorbed 10%, and dusts 1% (Memo, 1982f).

Generally, the considerations noted above (more detailed information for specific uses and assumptions concerning actual use practices, including protective clothing where appropriate) reduce the levels of exposure estimated in PD 4 from those estimated in PD 2/3 for most use patterns. The specifics of each assumption used in this document, and the reasons for any modifications of the PD 2/3 assumptions, are presented, in detail, in the Exposure Assessment (Appendix III).

Lindane has so many uses that exposure estimates could only be calculated for a representative subset, which, however, accounts for most identifiable usage of lindane. Because of this, and to provide a framework for regulating new uses in the future, the Agency has categorized the results of the exposure analysis in PD 4 according to the application method used. In the case of lindane, application methods correlate highly with risk, so categorizing uses in this way provides a rational regulatory perspective.

Exposure situations (excluding dietary exposure) are divided into the following categories (forestry, homeowner ornamentals, and foliar applications to Christmas trees)

3. Structural treatments (subterranean termites, powder post beetles)
4. Dip applications (hardwood logs and lumber, livestock dips, dog dips and shampoos)
5. Enclosed area sprays (moth sprays, uninhabited building and storage bin sprays)
6. Dust applications (seed treatment, dog dusts)
7. Below-shoulder spray applications (cucurbits)
8. Pre-plant soil applications (pineapples, sugar cane*)
9. Other household products (flea collars, shelf paper, household sprays).

Comparison of PD 2/3 with PD 4 annual exposure estimates for each use are presented in Table 3. Estimated daily exposures are presented in Table 4.

A narrative describing the details of the Agency's final non-dietary exposure analysis may be found in Appendix III (EPA 1982b). It provides summaries of EPA's PD 2/3 analyses, comments received regarding those analyses, revised assumptions, and estimates of exposure for each of the lindane uses. Tables showing details of the PD 4 calculations are not reprinted here, but are available upon request (EPA 1982b.)

NRDC (1983) charges that the estimated exposures to lindane have been substantially decreased between PD 2/3 and PD 4; that the studies upon which these changes were based are not generally adequate or relevant (and therefore, new exposure studies should be required); that assumptions were based on comments rather than new evidence; and that the reduced exposure estimates "artificially reduced the true risks of lindane use...." The agency disagrees with NRDC's assessment of the seven studies received in response to PD 2/3. These have been evaluated and found to be adequate for exposure estimates and certainly are more sound than some of the theoretical worst case assumptions which were used in PD 2/3. Any changes in assumptions, such as end-use dilutions, were based on comments and subsequent confirmation from pesticide labels, conversations with experts outside the Agency, etc. For the record, 19 of 29 exposures (not 23 of 29) were reduced, 2 remained the same, and 8 increased. The Agency rejects the contention that exposure estimates were "artificially" reduced and stands by its estimates as more accurate and realistic.

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* Sugar cane is not a currently registered use of lindane, but its use on sugar cane has been allowed as a Section 18 emergency use.

## TABLE 3

### USE BY USE SUMMARY OF ESTIMATED ANNUAL EXPOSURE* (MG/YEAR)[1] TO LINDANE: RESULTS OF PD 2/3 COMPARED WITH PD 4

|  | PD 2/3 |  |  |  | PD 4 |  |
|---|---|---|---|---|---|---|
|  | WITHOUT PROTECTIVE CLOTHING |  | WITHOUT PROTECTIVE CLOTHING |  | WITH PROTECTIVE CLOTHING |  |
|  | Dermal[1] | Respiratory | Dermal[1] | Respiratory | Dermal[1] | Respiratory[2] |
| **ABOVE SHOULDER SPRAYS**<br>**AIR BLAST or POWER HAND GUN** |  |  |  |  |  |  |
| ORNAMENTALS (commercial) | 90-3600 | 0.5-22 | N/A[3] | N/A | 40 | 0.24 |
| AVOCADOS | 800 | 1.6 | 320 | 0.6 | 64 | 0.6 |
| PECANS | 395 | 0.8 | 160 | 0.3 | 32 | 0.3 |
| LIVESTOCK | 6.5 | 0.04 | N/A | N/A | 7.9 | 0.01 |
| **ABOVE-SHOULDER SPRAYS**<br>**BACKPACK or HAND PRESSURE** |  |  |  |  |  |  |
| ORNAMENTALS (homeowners) | 30 | 0.10 | 3.6 | 0.02 | 0.7 | 0.02 |
| FORESTRY | 2400 | 16 | N/A | N/A | 56 | 0.3 |
| CHRISTMAS TREES (foliar) | 810 | 2.7 | N/A | N/A | 5.4 | 0.02 |
| **CRAWL SPACE TREATMENTS** |  |  |  |  |  |  |
| STRUCTURES |  |  |  |  |  |  |
| Applicators | 5600-11200 | 20-40 | N/A | N/A | 0.5 | 0.3 |
| Residents | 4/ | 60 | -- | 1.4<br>(once in 10 yrs) | N/A | N/A |

---

1. Dermal exposure estimate is not multiplied by skin absorption factor. This is factored into risk estimates by Toxicology Branch.
2. Where respiratory values in the "with protective clothing" column do not differ from the respiratory estimate "without protective clothing", it is because respiratory protection is not required and has not been factored in.
3. N/A - Not Applicable
4. -- = negligible
5. ND - Not Determined

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TABLE 3 (Continued)

USE BY USE SUMMARY OF ESTIMATED ANNUAL EXPOSURE (MG/YEAR)1/ TO LINDANE: RESULTS OF PD 2/3 COMPARED WITH PD 4

|  | PD 2/3 |  | PD 4 |  |  |  |
|---|---|---|---|---|---|---|
|  | WITHOUT PROTECTIVE CLOTHING |  | WITHOUT PROTECTIVE CLOTHING |  | WITH PROTECTIVE CLOTHING |  |
|  | Dermal1/ | Respiratory | Dermal1/ | Respiratory | Dermal1/ | Respiratory2/ |
| **DIPS** |  |  |  |  |  |  |
| HARDWOODS | 32,000 | 100 | N/A | N/A | -- | 16.0 |
| DOG DIPS |  |  |  |  |  |  |
| Applicators | 0.3 | -- | 11.1 | -- | 2 | -- |
| Post-treatment Exposure | -- | $0.9x10^{-5}$ to $2.7x10^{-4}$ | -- | 0.02 | N/A | N/A |
| DOG SHAMPOOS |  |  |  |  |  |  |
| Applicators | 51.4 | -- | 10.5 | -- | 2.1 | -- |
| Post-treatment Exposure | -- | 0.03-0.1 | -- | 0.02 | N/A | N/A |
| **ENCLOSED AREA SPRAYS** |  |  |  |  |  |  |
| MOTH SPRAYS |  |  |  |  |  |  |
| Applicators | -- | 0.10 | 3.3 | 2.3 | 0.7 | 2.3 |
| Employees | -- | 1.4 | -- | 1.4 | N/A | N/A |
| FUMIGATION DEVICES | -- | 149 | -- | 6.4 | N/A | N/A |
| UNINHABITED BUILDING & STORAGE BIN SPRAYS | -- | 10.7 | 0.5 | 0.02 | 0.1 | 0.02 |

1. Dermal exposure estimate is not multiplied by skin absorption factor. This is factored into risk estimates by Toxicology Branch.
2. Where respiratory values in the "with protective clothing" column do not differ from the respiratory estimate "without protective clothing", it is because respiratory protection is not required and has not been factored in.
3. N/A = Not Applicable
4. -- = negligible
5. ND - Not Determined

TABLE 3 (Continued)

**USE BY USE SUMMARY OF ESTIMATED ANNUAL EXPOSURE (MG/YEAR)[1] TO LINDANE: RESULTS OF PD 2/3 COMPARED WITH PD 4**

| | PD 2/3 | | | | PD 4 | |
|---|---|---|---|---|---|---|
| | WITHOUT PROTECTIVE CLOTHING | | WITHOUT PROTECTIVE CLOTHING | | WITH PROTECTIVE CLOTHING | |
| | Dermal[1] | Respiratory | Dermal[1] | Respiratory | Dermal[1] | Respiratory[2] |
| **DUSTS** | | | | | | |
| SEED TREATMENT | | | | | | |
| Applicators | 306 | 7.7 | N/A | N/A | 1.3 | 0.012 |
| Seed Sowing | ND[3] | ND | -- | 0.23 | N/A | N/A |
| DOG DUSTS | | | | | | |
| Applicators | 191 | 0.1 | 3 | 0.004 | 0.6 | 0.004 |
| Post-treatment Exposure | -- | 2.53 | -- | 0.04 | N/A | N/A |
| **BELOW SHOULDER SPRAYS** | | | | | | |
| CUCURBITS | 4.7 | 0.01 | 0.4 | 0.001 | 0.08 | 0.001 |
| CHRISTMAS TREES (stump/slash) | 87/27 | 1.8/0.2 | N/A | N/A | 11 | 0.3 |
| **INJECTABLE OR PREPLANT SOIL APPLICATIONS** | | | | | | |
| PINEAPPLES | -- | $7 \times 10^{-6}$ | -- | $7 \times 10^{-6}$ | N/A | N/A |
| **HOUSEHOLD PRODUCTS (OTHER)** | | | | | | |
| FLEA COLLARS | -- | 0.045 | -- | 0.3 | N/A | N/A |
| SHELF PAPER | -- | 5 | -- | 0.1 | N/A | N/A |
| HOUSEHOLD SPRAYS | | | | | | |
| Applicators | -- | $1 \times 10^{-5}$ | 0.3 | 0.2 | 0.06 | 0.2 |
| Residents | ND | ND | -- | 0.02 | N/A | N/A |

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1. Dermal exposure estimate is not multiplied by skin absorption factor. This is factored into risk estimates by Toxicology Branch.

## B. Dietary Exposure to Lindane

More detailed information on the Agency's assessment of dietary risks from lindane may be found in a document prepared by EPA's Environmental Fate Branch (EPA, 1981b).

### 1. The Agency's PD 2/3 Calculations

The Agency, in calculating an estimate of the dietary exposure of the general population to lindane, used data showing average lindane residues for 12 composite food group categories from the FDA market basket (Total Diet Composites) survey during the period from 1972 to 1975 (EPA, 1978). From this average, the daily intake of lindane in mg/1.94 kg diet for each composite category was calculated, then totaled to get the average daily exposure for all 12 food categories. This daily intake average was estimated to be 0.00266 mg/1.94 kg diet/day, which equals 0.038 ug/kg bw/day for a 70 kg adult.

### 2. Comment on the Agency's Calculation of Dietary Exposure

The Centre International d'Etudes du Lindane (rebuttal #94), represented by C. Edwards, agreed that the use of the market basket survey data was appropriate, but that more recent available market basket data should have been used. Also, Edwards disagreed with the way certain FDA numbers were evaluated by EPA, primarily that trace values were assigned a value of 0.004 parts per million (ppm), when analytical techniques quantified residues considerably less than 0.004 ppm.

Imported dairy products, according to Edwards, contained the largest proportion of total lindane residues up to 1975. In more recent years, however, sugar and its adjuncts have had larger residues, with residues in meat and poultry remaining fairly constant. Edwards suggested that contamination of food storage bins was a likely source of lindane residues.

NRDC (1983) disagrees with with the Agency's estimate of dietary exposure with respect to the use of the 1976-1980 FDA data and the assignment of a zero value to trace residues. The Agency agrees that the complete data base from the FDA Market Basket Survey should be used in estimating dietary exposure to lindane. The Agency has amended its PD 2/3 estimate to reflect the entire data base. However, the Agency disagrees on the issue of trace residues. These points are addressed in B. 3. below.

### 3. The Agency's PD 4 Response

The Agency agrees that the most current FDA market basket data (Total Diet Composites) as well as historical data should be used to evaluate lindane residues in the diet of the general population. Data from 1964-1980 may be found in Table 5. With the exception of 1974, the residues of lindane in the diet in recent years (FY 1973 to FY 1980) have remained relatively constant, using FDA's methods of data evaluation. However, the Agency has now used the entire data base as well as the most recent (1976-1980) data to arrive at a range of exposure estimates.

TABLE 4

DAILY EXPOSURE TO LINDANE

| | EXPOSURE WITHOUT PROTECTIVE CLOTHING: (mg/kg bw/day) | | | EXPOSURE WITH PROTECTIVE CLOTHING: (mg/kg bw/day) | |
|---|---|---|---|---|---|
| | DAYS EXPOSED/YR | DERMAL | RESPIRATORY | DERMAL | RESPIRATORY1/ |
| **ABOVE SHOULDER SPRAYS AIR BLAST or POWER HAND GUN** | | | | | |
| ORNAMENTALS (commercial) | 4 | N/A1/ | N/A | 0.17 | $8.6 \times 10^{-4}$ |
| AVOCADOS | 2 | 2.3 | $4.6 \times 10^{-3}$ | 0.46 | $4.6 \times 10^{-3}$ |
| PECANS | 1 | 2.3 | $4.6 \times 10^{-3}$ | 0.46 | $4.6 \times 10^{-3}$ |
| LIVESTOCK | 1 | N/A | N/A | 0.11 | $1.5 \times 10^{-4}$ |
| **ABOVE-SHOULDER SPRAYS BACKPACK or HAND PRESSURE** | | | | | |
| ORNAMENTALS (homeowners) | 1 | $5.1 \times 10^{-2}$ | $3 \times 10^{-4}$ | $1 \times 10^{-2}$ | $3 \times 10^{-4}$ |
| FORESTRY | 30 3/ | N/A | N/A | $3.7 \times 10^{-2}$ | $1.3 \times 10^{-4}$ |
| CHRISTMAS TREES (foliar) | 1 | N/A | N/A | $7.0 \times 10^{-2}$ | $2.3 \times 10^{-3}$ |
| **CRAWL SPACE TREATMENTS** | | | | | |
| STRUCTURES | | | | | |
| Applicators | 5 | N/A | N/A | $1.5 \times 10^{-3}$ | $7.7 \times 10^{-4}$ |
| Residents | 36/yr 3/ (once every 10 yr) | N 2/ | $6.9 \times 10^{-4}$ | N/A | N/A |

1. N/A is used for Not Applicable. Calculations were made for "No Protective Clothing" only in cases where none is worn or there is doubt about whether or not it is worn. Similary, calculations were not made for protective clothing if the situation does not apply.

2. N is used for Negligible Exposure.

3. Subchronic exposure based on 5 mg/kg/day NOEL (See VII., C.).

4. Chronic exposure based on 1.25 mg/kg/day NOEL (See VII., C.).

TABLE 4 (Continued)

DAILY EXPOSURE TO LINDANE

|  | EXPOSURE WITHOUT PROTECTIVE CLOTHING: (mg/kg bw/day) |  |  | EXPOSURE WITH PROTECTIVE CLOTHING: (mg/kg bw/day) |  |
|---|---|---|---|---|---|
|  | DAYS EXPOSED/YR | DERMAL | RESPIRATORY | DERMAL | RESPIRATORY |
| E |  |  |  |  |  |
| SEED TREATMENT |  |  |  |  |  |
| Applicators | 2 | N/A | N/A | 9.3 x $10^{-3}$ | 8.6 x $10^{-3}$ |
| Seed Sowing | 2 | N | 1.7 x $10^{-3}$ | N/A | N/A |
| DOG DUSTS |  |  |  |  |  |
| Applicators | 2 | 2 x $10^{-2}$ | 3 x $10^{-5}$ | 4 x $10^{-3}$ | 3 x $10^{-5}$ |
| Post-treatment Exposure | 6 | N | 8.4 x $10^{-5}$ | N/A | N/A |
| M SHOULDER SPRAYS |  |  |  |  |  |
| CUCURBITS | 3.5 | 1.7 x $10^{-3}$ | 4 x $10^{-6}$ | 3.4 x $10^{-4}$ | 4 x $10^{-6}$ |
| CHRISTMAS TREES (stump slash/trunk) | 1 | N/A | N/A | 0.18 | 4.5 x $10^{-3}$ |
| ANT SOIL APPLICATIONS |  |  |  |  |  |
| PINEAPPLES | 1 | N | 9.7 x $10^{-8}$ | N/A | N/A |
| HOLD PRODUCTS (OTHER) |  |  |  |  |  |
| FLEA COLLARS | 365 a/ | N | 9.8 x $10^{-6}$ | N/A | N/A |
| HELF PAPER | 365 a/ | N | 3.9 x $10^{-5}$ | N/A | N/A |
| OUSEHOLD SPRAYS |  |  |  |  |  |
| Applicators | 1 | 4.8 x $10^{-3}$ | 3.2 x $10^{-3}$ | 9 x $10^{-6}$ | 3.2 x $10^{-3}$ |
| Residents | 3 | N | 6.6 x $10^{-5}$ | N/A | N/A |

TABLE 4 (CONTINUED)

DAILY EXPOSURE TO LINDANE

| | EXPOSURE WITHOUT PROTECTIVE CLOTHING: (mg/kg bw/day) | | | EXPOSURE WITH PROTECTIVE CLOTHING: (mg/kg bw/day) | |
|---|---|---|---|---|---|
| | DAYS EXPOSED/YR | DERMAL | RESPIRATORY | DERMAL | RESPIRATORY |
| **DIPS** | | | | | |
| HARDWOOD LOGS & LUMBER | 200[4/] | N/A | N/A | N | $1.3 \times 10^{-3}$ |
| DOG DIPS | | | | | |
| Veterinarians | 26[3/] | $6.1 \times 10^{-3}$ | N | $1.2 \times 10^{-3}$ | N |
| Post-treatment Exposure to owners | 3 | N | $8.6 \times 10^{-5}$ | N/A | N/A |
| DOG SHAMPOOS | | | | | |
| Applicators | 1 | 0.16 | N | $3 \times 10^{-2}$ | negligible |
| Post-treatment Exposure | 3 | N | $9.6 \times 10^{-6}$ | N/A | N/A |
| **ENCLOSED AREA SPRAYS** | | | | | |
| MOTH SPRAYS | | | | | |
| Applicators | 26[3/] | $1.0 \times 10^{-3}$ | $1.3 \times 10^{-3}$ | $3.6 \times 10^{-4}$ | $1.3 \times 10^{-3}$ |
| Employees | 78[3/] | N | $9 \times 10^{-8}$ | N/A | N/A |
| FUMIGATION DEVICES | 48 | N | $1.8 \times 10^{-3}$ | N/A | N/A |
| UNINHABITED BUILDING & STORAGE BIN SPRAYS | 12[3/] | $6.2 \times 10^{-4}$ | $3.9 \times 10^{-8}$ | $1.2 \times 10^{-4}$ | $2.9 \times 10^{-5}$ |

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## TABLE 5

### AVERAGE DAILY INTAKES OF LINDANE IN FDA TOTAL DIET COMPOSITES FROM FY 1964 - FY 1980

| YEARS | RESIDUE INTAKE (ug/kg bw/day) | SOURCE OF DATA |
|---|---|---|
| 1964-1969 | 0.0500 (total) | EPA Position Document 1<br>DHEW Total Diet Studies |
| 1973 | 0.0032 | " |
| 1974 | 0.0084 | " |
| 1975 | 0.0031 | FDA Total Diet Composites |
| 1976 | 0.0025 | " |
| 1977 | 0.0039 | " |
| 1978 | 0.0024 | " |
| 1979 | 0.0038 | " |
| 1980 | 0.0028 | |

Quantitative residues, at the limit of detection, are subject to a high degree of unreliability. Therefore, consistant with FDA's analyses, the Agency did not assign a numerical value to trace findings. In addition, assigning the trace findings a value of .004 ppm would not substantially alter the exposure estimates shown below.

EPA agrees that imported dairy products contained the [illegible]rtion of lindane residues up to 1975, but that in more recent ye[illegible]s and adjuncts have had the largest proportion of residues. Residues in meat and poultry have remained fairly constant. EPA agrees that lindane use in empty storage bins could be a source of these lindane residues; however, the residues are not sufficiently large to be of concern.*

Using the FDA market basket surveys (Total Diet Composites) for the more recent period of FY 1976 - FY 1980, the average dietary intake is estimated to be 0.2141 ug/2.92 kg diet/day, which equals 0.0031 ug/kg bw/day for a 70 kg adult. This is a ten-fold reduction from the estimate used in PD 2/3. Using the entire FDA data base (1964-1980), the exposure is estimated to be 1.09 ug/day or 0.016 ug/kg/day. This is a twofold reduction from the estimate in PD 2/3.

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* The Agency will reassess the adequacy of lindane tolerances when

## V. BENEFITS

The lindane PD 2/3 was based on a benefit analysis completed in June of 1978 (EPA 1978) That analysis expressed economic impacts in 1975-76 dollars. Although it was not updated in PD 4 except for a few uses, the Agency assumes in its PD 4 risk-benefit analysis that the economic estimates are understated. That is, the nominal dollar measure of impacts is larger (due to inflation) for uses which have been stable or expanding.

A complete use-by-use summary of EPA's PD 2/3 benefits analysis, discussion of the comments received regarding benefits, and EPA's PD 4 final position on the benefits of lindane are contained in the Summary and Analysis of Benefits-Related PD 2/3 Comments (EPA, 1982c.) The following discussion provides a synopsis of that analysis and its conclusions.

The Agency received 141 comments in response to the PD 2/3. The majority of these addressed the high benefits and lack of alternatives for several key uses. Almost none of these comments provided new information with which to quantify the benefits, or new information about the existence of alternatives, but the Agency considers that the large number of comments may provide qualitative evidence of lindane's benefits. Many of the points made in the public comments were also raised in USDA's comments to the Agency (see Appendix I).

On a percentage basis, several uses accounted for the vast majority of the comments received:

Structural uses: Approximately 40% of the comments received addressed the structural use of lindane. Most cited the lack of acceptable alternatives for controlling powder post beetles, especially since chlordane, a substitute for lindane, was cancelled effective March 6, 1978. Fumigant alternatives are generally considered unsatisfactory due to application problems and extremely high expense. For these reasons, EPA concludes that the benefits of lindane are high for structural uses.

Seed treatment: Approximately 25% of the comments received addressed seed treatment uses of lindane. Again, most cited the lack of acceptable alternatives, and the usefulness of lindane as a control material. In spite of the large number of comments received, there was no substantive information to suggest that previous estimates of the benefits of this use were wrong, or that the benefits could be quantified. Most of the comments supported the Agency's PD 2/3 conclusion that cancellation of the use on small grains, lentils, and dry peas might cause major regional impacts at the user and market levels, but stated that these benefits had not been given adequate weight in the risk-benefit analysis. Since alternative treatments are available for the corn use, benefits are lower for this particular seed treatment use.

Ornamentals, forestry, and Christmas trees: Approximately 20% of the comments received addressed these three uses, all of which use lindane for control of wood borers. Lack of alternatives was frequently cited; other pesticides are registered for borer control but lindane is the only pesticide registered to control all borers on all woody ornamentals. Although alternatives are registered for control of bark beetles (cultural management, oxydemetonmethyl, endosulfan, dicrotophos, and chlorpyrifos), commentors claim that these are too expensive, ineffective, or relatively more toxic than lindane. Also, there are claims that lindane is the only pesticide which is effective once trees are already infested, but there is conflicting evidence on this point. The Agency concludes that cancellation could have major impacts on the woody ornamental industry; small, privately-owned, Southern forest areas; and Southern Christmas tree farms. Impacts on the florist and foliage industries, and cool-climate forest areas and Christmas tree farms, would probably be significant but less severe.

Animal uses: Approximately 15% of the comments received addressed uses on livestock and pets. Commentors claimed that restricting availability to pest-control operators and veterinarians would cause inconvenience, especially since toxaphene is the only equally effective alternative for controlling mites. None of the the comments suggested revision of the PD 2/3 benefit analysis, however, which projected minor impacts unless mites became an endemic problem.

Hardwood logs and lumber: Approximately 8% of the comments received addressed the hardwood logs and lumber use. Most attested to the usefulness and necessity of lindane for protection of hardwood lumber. CIEL (rebuttal #94) estimated that due to increased lumber prices, annual impacts were approximately $100 million larger than EPA had estimated. Another commentor stated that EPA had overlooked the availability of endosulfan as an alternative for this use (comment #134.) EPA acknowledges that the price of lumber and therefore the value of the hardwood use of lindane has increased, and that endosulfan is registered for this use. Although the dollar benefits could not be quantified, lindane is clearly a valuable control material for protection of hardwood logs and lumber.

Minor uses: EPA received several comments pointing out the considerable benefits of lindane use for minor uses which were not addressed in PD 2/3, including use for preserving historic artifacts, and use on sugar cane (the latter is currently allowed only as an emergency use). Although these are minor uses, EPA acknowledges that cancellation of lindane would have major impacts on efforts to protect historical artifacts, and on the sugar cane industry. EPA agrees that there are probably substantial benefits from these two uses of lindane, and perhaps from other uses which can not be analyzed separately. The magnitude of those benefits can not be quantified.

(Note: the percentages of comments received for the use categories above add to more than 100% because some comments addressed more than one use.)

A summary of the results of the PD 4 benefits analysis are as follows:

High benefit uses (no alternatives; significant impacts if cancelled):

- woody ornamentals, including Christmas trees (no alternatives to control wood borers)
- forestry (registered alternatives significantly more expensive and perhaps inefficacious against some pests)
- seed treatment (possibly major regional impacts)
- structures (alternatives significantly more expensive, inconvenient, and toxic)
- avocados (moderate impacts nationwide, but severe impacts in Florida)

- historic preservation (no alternatives against powder post beetles)
- hardwood logs and lumber (clearly valuable as a control method, although endosulfan is available)
- dog dips (many alternatives for most uses, but no equally effective alternative for treating scabies)

Moderate benefit uses (alternatives may be unavailable but impact if lindane were unavailable is minor, or alternatives are significantly more expensive, or alternatives are less efficacious)

- floral and foliage ornamentals (no alternatives for certain pests but cancellation would not cause major economic impacts)
- livestock dips (alternatives available but only toxaphene is equally effective against scabies);
- sugar cane (currently in use under emergency exemption provisions)
- pineapples (alternatives more expensive and less effective)

Low benefit uses (alternatives exist, or unavailability of lindane would result in only minor losses)

- cucurbits (numerous satisfactory alternatives)
- pecans (alternatives slightly more expensive)
- all household products except dog dips (numerous satisfactory alternatives)
- enclosed area sprays (numerous satisfactory alternatives)

## VI. SUMMARY of KEY RISK-BENEFIT CONSIDERATIONS

This chapter summarizes EPA's conclusions about the risks and benefits of lindane.

## A. Oncogenicity : Key Points

Several independent laboratory studies have been used to evaluate the oncogenic potential of lindane. The evidence that lindane is carcinogenic in mice is based on two lifetime studies, those by Thorpe and Walker and by NCI. Two subchronic studies by Goto et al. and Hanada et al. provide supportive evidence of oncogenicity. Primary responses were seen in the liver, an organ with high background tumor rates in the strains tested, but metastases to other organs were observed in some cases.

The scientific community is currently debating whether or not increased mouse liver tumors are predictive of human carcinogenicity, especially in the absence of positive mutagenicity data, or induction of primary tumors at other sites. One position is that such tumors provide suggestive evidence that the chemical may act by promoting carcinogenesis rather than acting as a "complete" carcinogen. Questions have been raised about the appropriateness of using linear risk extrapolation models (such as the linear multistage) for lindane where mouse liver tumors have been the primary carcinogenic response.

As indicated above, information regarding a chemical's mutagenic potential may provide valuable information for evaluating the mechanism by which that chemical may cause cancer. However, mutagenicity information on lindane is at this time inconclusive. More extensive short-term testing for genotoxicity could provide useful information on the mechanistic questions associated with lindane's oncogenic activity.

It is prudent for EPA to presume that any agent which causes tumors in animals has potential to cause carcinogenic effects in humans. For lindane the Agency has used quantitative risk estimates derived from the available mouse data, and has extrapolated risks using the linear, multistage model (See Table 6).

The risk numbers in PD 4 and PD 2/3 differ as a result of changes in the risk extrapolation procedure (i.e., the use of a 95% upper limit estimate), an interspecies scaling factor, and in exposure estimates. While this change in extrapolation procedure and inclusions of the scaling factor caused an increase in the potency estimate, the exposure estimates in most cases were decreased. Differences in the interpretations of the significance of those numbers are due to the fact that the Agency recognizes the uncertainties surrounding these estimates, as described above, and has developed its regulatory conclusions accordingly.

## B. Fetotoxicity/Reproductive Effects : Key Points

Lindane causes fetal effects in test animals only at or above doses which also cause general toxic effects in the mother. Therefore, protecting mothers from toxic effects will simultaneously protect fetuses from possible adverse effects. The NOEL for general toxic effects (anorexia and CNS effects) is 5 mg/kg/day.

Since the toxicologic effects observed at 5 mg/kg/day and below are reversible, (See Section III.A.2.6) a margin of safety somewhat less than 100 might be considered adequate to protect most exposed populations from the CNS effects. However, since fetal effects occur above 10 mg/kg/day, EPA concludes that a margin of safety of more than 100 for these effects is attained for all uses and specific warnings or restrictions are not necessary.

## C. Acute Hazards to Humans and Domestic Animals

Information available from reproductive an chronic toxicology studies, specific neurological studies, and clinical investigations suggest that the NOEL for acute CNS effects is around 5 mg/kg/day. Most of the animal studies that investigate lindane's neurological effects are more specific than conventional screening studies, and they suggest lower no-effect levels for specific nerve functions in comparison to the more generalized toxicity tests.

Based on these considerations, the Agency believes that the 5 mg/kg/day NOEL is an adequate no-effect level with respect to acute CNS effects. It is unlikely that lindane causes permanent neurological damage at the levels and conditions under which humans will be exposed.

## D. Susceptibility of Children

In view of the results reported by Hanig et al. (1976), and the episodes involving lindane and children, and additional comments and data , the Agency is still concerned that children may be more susceptible to the toxic effects of lindane. As stated previously by the Agency, there is still insufficient data on which to base separate Margin Of Safety calculations for children.

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E. Possible Association Between Lindane and Blood Dyscrasias:

Several case studies, cited by the Agency in PD 1, indicated that blood dyscrasias might be associated with exposure to lindane. However, these cases do not satisfy epidemiologic criteria for establishing a cause-effect relationship between lindane exposure and blood dyscrasias.

A recent epidemiology study (Morgan 1980) in Iowa showed no correlation between lindane blood levels and the occurrence of adverse hematologic effects. However, because blood dyscrasias are extremely rare, the study size was not large enough to provide statistically significant results. In conclusion, available epidemiological data on lindane do not establish a cause-effect relationship between lindane and blood dyscrasias.

F. Acute Toxicity to Aquatic Wildlife

Lindane is known to be quite toxic to aquatic wildlife, but is not presently registered for direct aquatic application. Therefore, the chief concern is to avoid application, handling, or disposal practices which could result in significant drift or runoff into water, such as aerial application or improper disposal.

G. Key Points in the Exposure Analysis

The exposure estimates used in the original PD 2/3 analysis were purposefully conservative, since they were based on highly uncertain information and EPA prefers in such cases to err on the side of safety. Since the proposed decision was published, EPA has been able to improve its estimates significantly. Some of the revisions in PD 4 are based on new information, while others are based on the use of better surrogate data. Details of all the changes in the exposure analysis and the reasons for them may be found in Appendix III. Table 3 compares the exposure calculations in PD 2/3 with those in PD 4.

Dietary exposures are estimated to be low. The estimates are based on actual residue monitoring data. Lindane is one of a comparatively few compounds for which considerable historic and current monitoring data exist. In light of 1) the current use patterns of lindane, 2) of current label application restrictions and directions, and 3) of actual monitoring data, the Agency believes dietary exposures are low.

In general, dermal exposure is by far the most significant route of exposure to humans. Certain application methods involve significantly more exposure (and therefore risk) than others. Overhead spraying, fumigation, and dipping tend to have the highest exposures associated with them. Mixer/loaders are also known to be exposed to high active ingredient concentrations, but their exposure levels were not separately calculated. Total exposure varies according to duration of exposure and not just application method.

## H. Key Points in the Benefits Analysis

The considerable benefits of lindane's use are given more weight in the PD 4 decision than the PD 2/3 proposal, as was suggested in the many compelling comments which the Agency received from the numerous parties. The decision proposed in 1980 was criticized by the U.S. Department of Agriculture, the Scientific Advisory panel, and the public, for not adequately considering lindane's benefits. The Agency agrees that the benefits were not adequately considered in its original assessment, and has revised the risk/benefit analysis accordingly.

The highest benefit uses are those for which the use is economically important and there are no alternatives. These include uses against wireworms (seed treatment), all uses against wood borers (forestry, woody ornamentals, Christmas trees, hardwoods, structures, and historic preservation), treatment of scabies (livestock and dog dips), and treatment of mirids on avocados.

All the other agricultural uses have moderate benefits except for pecans and cucurbits, for which numerous alternative pest control methods are available.

Low benefit uses include pecans, cucurbits, enclosed area sprays and all household uses except dog dips.

# VII. RISK-BENEFIT ANALYSES

## A. General notes

The process of balancing risks and benefits is difficult and necessarily subjective. EPA is required by FIFRA to insure that pesticides do not present "unreasonable risk". A finding of "unreasonable risk" means that the risks outweigh the benefits, and that available risk reduction measures, short of cancellation, cannot lower these risks sufficiently to insure that the benefits outweigh them. In most cases, risk reduction measures short of cancellation are sufficient to bring the risks and benefits to a reasonable balance, and they are required for that purpose.

EPA's final decision on the pesticidal uses of lindane, presented in this chapter, gives more consideration to the benefits and the regulatory options short of cancellation than the PD 2/3. It is also based on significantly better information than the decision proposed in 1980. The final decision has been carefully designed to insure that immediate but minimally burdensome steps will be taken to protect any populations which may be at risk, to preserve the benefits of lindane's use, and to insure that uncertainties surrounding certain of the risks will be reduced within a reasonable time frame.

In this chapter, risk-benefit considerations for six use groups are presented. The groups were categorized by application methodology, which correlates well with exposure and also risk.

The phrases "without protective clothing" and "with protective clothing" occur repeatedly in the discussions regarding exposure. "No protective clothing" means that EPA assumes that the applicator's head is uncovered, and that a v-necked t-shirt and pants are worn. "Protective clothing" varies for each use; the reader may refer to the Exposure Analysis Narrative (Appendix III) for use-by-use descriptions, unless otherwise indicated.

## B. Interpreting the quantitative cancer estimates

The risk estimates discussed below must be interpreted according to the perspectives discussed in earlier parts of this document. As was noted earlier, the evidence that lindane is carcinogenic in mice is based on two lifetime studies, Thorpe and Walker and the NCI study. Both studies show that oral administration of lindane causes hepatic tumors. However, in the best carcinogenicity study, Thorpe and Walker, only a single dose of lindane was tested. Two subchronic studies in mice, Goto et al. and Hanada et al., provide supportive evidence consistent with that found in the two lifetime studies. In addition, 2,4,6 trichlorophenol, a metabolite of lindane, is carcinogenic in rats and mice. Mutagenicity testing in lindane is indeterminate and does not allow the Agency to confirm or refute the genotoxicity of this chemical. Based on the information above, the linearized, multi-stage model was used to provide an upper limit risk estimate of potential human risk.

Another uncertainty exists due to the fact that the cancer risk estimates are based on an assumption of lifetime exposure to lindane. Except in cases where people are exposed for a lifetime (the Agency assumes 35 years for applicator exposure and 70 years for household product exposures), these estimates tend to overstate the actual risks.

In spite of these uncertainties, EPA presumes that a chemical which has the ability to cause tumors in animals has the potential to cause carcinogenic effects in humans. The Agency also assumes that some people may be exposed to the chemical over their entire lifetimes. Both of these assumptions are based on the desire to make estimates which are expected to err in favor of protecting human health. However, the uncertainties are taken into account in a qualitative sense in the risk-benefit analysis.

These facts mean that the quantitative cancer risk estimates discussed below are subject to significant uncertainty. Thus, although these numbers are based on the best information available at this time, they may be subject to a margin of error of at least one order of magnitude in either direction. It is expected that the actual risks are lower than the estimates obtained using linear models. The Agency therefore uses these estimates primarily for determining relative risk levels from one use group to another, and to show the upper bound of potential risk.

## C. Margin of Safety Estimates

The considerations discussed in Chapter II lead the Agency to conclude that a no-observed effect level (NOEL) of 5 mg/kg/day is appropriate for general toxicity while a NOEL of 10 mg/kg/day is appropriate for fetotoxic effects.

Another of lindane's possible effects, which may correspond with the general toxicological effects, is increased liver weight. The EPA did not (critically) review in detail the many chronic and sub-chronic studies which have shown liver weight increases in test animals because this effect was not related to an RPAR criterion discussed on PD 2/3. However, a general review of the literature shows that 1.25 mg/kg/day is the NOEL with respect to liver weight increases from chronic exposure (Burnam, 1982).

Margins of safety (MOS) for general toxicity, fetal effects in the presence of general toxicity, and chronic liver toxicity (enlargement) are calculated by dividing the NOEL by exposure, expressed as mg/kg/day. Table 2 lists MOS values. For fetotoxicity, these MOS values can be doubled for most uses based on a 5 mg/kg NOEL. The hardwood logs and lumber, flea collars, and shelf paper uses involve chronic exposures and a NOEL of 1.25 mg/kg was used to calculate the MOS for these three uses.

## D. Risk/Benefit Summary Tables

Table 6 summarizes all the information used in the risk-benefit analysis: the quantitative risk calculations, qualitative benefits calculations, and exposed populations ("cohort at risk"). Table 7 summarizes the same information, but for PD 2/3; it may be used to compare the risk and benefit conclusions of the PD 2/3 with the PD 4.

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## TABLE 6

## USE BY USE SUMMARY OF ESTIMATED LINDANE RISKS AND BENEFITS

| USE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY[1] (Gen'l Tox. and Fetal Effects) W/out prot. cloth. | MARGIN OF SAFETY[1] (Gen'l Tox. and Fetal Effects) with prot. cloth. | CANCER RISK[2] W/out prot. cloth. | CANCER RISK[2] with prot. cloth. | Protective clothing worn routinely? |
|---|---|---|---|---|---|---|---|
| **ABOVE SHOULDER SPRAYS** AIR BLAST or POWER HAND GUN | | | | | | | |
| ORNAMENTALS (commercial) | high | 600 | N/A[3] | 280 | N/A | $1.1 \times 10^{-4}$ | yes |
| AVOCADOS | high | ? | 22 | 99 | $6.9 \times 10^{-4}$ | $1.5 \times 10^{-4}$ | no |
| PECANS | low | 1,200 | 21 | 99 | $3.5 \times 10^{-4}$ | $7.4 \times 10^{-5}$ | no |
| LIVESTOCK | medium | 240,000 | N/A | 440 | N/A | $1.7 \times 10^{-5}$ | yes |
| **ABOVE SHOULDER SPRAYS** BACKPACK or HAND PRESSURE | | | | | | | |
| ORNAMENTALS (homeowners) | high | 75,000 | 936 | 3846 | $8.1 \times 10^{-6}$ | $1.9 \times 10^{-6}$ | no |
| FORESTRY | high | 1,000 | N/A | 1767 | N/A | $1.2 \times 10^{-4}$ | yes |
| CHRISTMAS TREES (foliar) | high | 10,000 | N/A | 500 | N/A | $1.2 \times 10^{-5}$ | yes |
| **CRAWL SPACE TREATMENTS** | | | | | | | |
| STRUCTURES | | | | | | | |
| Applicators | high | 8,000 | N/A | 5435 | N/A | $7.4 \times 10^{-6}$ | yes |
| Residents | high | ? | 7246 | N/A | $5.9 \times 10^{-6}$ | N/A | no |

1. Calculated using expected daily exposures.
2. Calculated using expected annual exposures.
3. Not Applicable. Calculations were made for "No Protective Clothing" only in cases where none is worn or there is doubt about whether or not it is worn. Similarly, calculations were not made for protective clothing if the situation does not apply.

## TABLE 6 (Continued)

## USE BY USE SUMMARY OF ESTIMATED LINDANE RISKS AND BENEFITS

| USE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY[1] (Gen'l Tox. and Fetal Effects) |  | CANCER RISK[2] |  | Protective clothing worn routinely? |
|---|---|---|---|---|---|---|---|
|  |  |  | w/out prot. cloth. | with prot. cloth. | w/out prot. cloth. | with prot. cloth. |  |
| **DIPS** |  |  |  |  |  |  |  |
| HARDWOOD LOGS & LUMBER | high | D-840 [4]<br>R-2400[5] | N/A | 962 | N/A | $3.6 \times 10^{-4}$ | yes |
| DOG DIPS |  |  |  |  |  |  |  |
| Applicators |  |  |  |  |  |  |  |
| Veterinarians | medium | 130,000 | 8197 | 71667 | $2.4 \times 10^{-5}$ | $4.2 \times 10^{-6}$ | no |
| Post-treatment Exposure to owners | medium | 15,000,000 | 58140 | N/A | $4.2 \times 10^{-7}$ | N/A | no |
| DOG SHAMPOOS |  |  |  |  |  |  |  |
| Applicators | low | ? | 312 | 1563 | $2.2 \times 10^{-5}$ | $4.5 \times 10^{-6}$ | no |
| Post-treatment Exposure | low | ? | 58140 | N/A | $4.2 \times 10^{-7}$ | N/A | no |
| **ENCLOSED AREA SPRAYS** |  |  |  |  |  |  |  |
| MOTH SPRAYS |  |  |  |  |  |  |  |
| Applicators | low | ? | 3378 | 37425 | $5.6 \times 10^{-5}$ | $5 \times 10^{-5}$ | no |
| Employees | low | ? | 55556 | N/A | $3 \times 10^{-5}$ | N/A | no |
| FUMIGATION DEVICES | low | ? | 2631 | N/A | $1.4 \times 10^{-4}$ | N/A | no |
| UNINHABITED BUILDING & STORAGE BIN SPRAYS | low | ? | 54945 | 121,957 | $1.5 \times 10^{-6}$ | $6.4 \times 10^{-7}$ | no |

4. "D" represents dermal exposure.
5. "R" represents respiratory exposure.

TABLE 6 (Continued)

USE BY USE SUMMARY OF ESTIMATED LINDANE RISKS AND BENEFITS

| USE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY[1] (Gen'l Tox. and Fetal Effects) |  | CANCER RISK[2] |  | Protective clothing worn routinely? |
|---|---|---|---|---|---|---|---|
|  |  |  | w/out prot. cloth. | with prot. cloth. | w/out prot. cloth. | with prot. cloth. |  |
| **DIPS** |  |  |  |  |  |  |  |
| HARDWOOD LOGS & LUMBER | high | D-840 [4]<br>R-2400[5] | N/A | 962 | N/A | $3.6 \times 10^{-4}$ | yes |
| DOG DIPS |  |  |  |  |  |  |  |
| Applicators |  |  |  |  |  |  |  |
| Veterinarians | medium | 130,000 | 8197 | 71667 | $3.4 \times 10^{-5}$ | $4.2 \times 10^{-6}$ | no |
| Post-treatment Exposure to owners | medium | 15,000,000 | 58140 | N/A | $4.2 \times 10^{-7}$ | N/A | no |
| DOG SHAMPOOS |  |  |  |  |  |  |  |
| Applicators | low | ? | 312 | 1562 | $2.2 \times 10^{-5}$ | $4.5 \times 10^{-6}$ | no |
| Post-treatment Exposure | low | ? | 58140 | N/A | $4.2 \times 10^{-7}$ | N/A | no |
| **ENCLOSED AREA SPRAYS** |  |  |  |  |  |  |  |
| MOTH SPRAYS |  |  |  |  |  |  |  |
| Applicators | low | ? | 3378 | 37425 | $5.6 \times 10^{-5}$ | $5 \times 10^{-5}$ | no |
| Employees | low | ? | 55556 | N/A | $3 \times 10^{-5}$ | N/A | no |
| FUMIGATION DEVICES | low | ? | 2631 | N/A | $1.4 \times 10^{-4}$ | N/A | no |
| UNINHABITED BUILDING & STORAGE BIN SPRAYS | low | ? | 54945 | 121,957 | $1.5 \times 10^{-6}$ | $6.4 \times 10^{-7}$ | no |

4. "D" represents dermal exposure.
5. "R" represents respiratory exposure.

TABLE 6 (Continued)

USE BY USE SUMMARY OF ESTIMATED LINDANE RISKS AND BENEFITS

| USE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY1/ (Gen'l Tox. and Fetal Effects) w/out prot. cloth. | MARGIN OF SAFETY1/ (Gen'l Tox. and Fetal Effects) with prot. cloth. | CANCER RISK2/ w/out prot. cloth. | CANCER RISK2/ with prot. cloth. | Protective clothing worn routinely? |
|---|---|---|---|---|---|---|---|
| **DUSTS** | | | | | | | |
| SEED TREATMENT | | | | | | | |
| Applicators | high | 130,000 | N/A | 5000 | N/A | $3 \times 10^{-6}$ | yes |
| Seed Sowing | high | 130,000 | 3941 | N/A | $4.9 \times 10^{-6}$ | N/A | no |
| DOG DUSTS | | | | | | | |
| Applicators | low | ? | 2763 | 11628 | $6.4 \times 10^{-6}$ | $1.4 \times 10^{-6}$ | no |
| Post-treatment Exposure | low | ? | 58140 | N/A | $4.2 \times 10^{-7}$ | N/A | no |
| **BELOW SHOULDER SPRAYS** | | | | | | | |
| CUCURBITS | low | 950 | 29736 | 131579 | $8.7 \times 10^{-7}$ | $1.9 \times 10^{-7}$ | no |
| CHRISTMAS TREES (stump/slash) | high | 10,000 | N/A | 256 | N/A | $3 \times 10^{-5}$ | yes |
| **PREPLANT SOIL APPLICATIONS** | | | | | | | |
| PINEAPPLES | medium | 1600 | 1000000 | N/A | $1.5 \times 10^{-10}$ | N/A | no |
| **HOUSEHOLD PRODUCTS (OTHER)** | | | | | | | |
| FLEA COLLARS | low | ? | 143349 | N/A | $4.2 \times 10^{-6}$ | N/A | no |
| SHELF PAPER | low | 11,000,000 | 725000 | N/A | $2.1 \times 10^{-6}$ | N/A | no |
| HOUSEHOLD SPRAYS | | | | | | | |
| Applicators | low | ? | 1370 | 1520 | $4.9 \times 10^{-6}$ | $4.4 \times 10^{-6}$ | no |
| Residents | low | ? | 55556 | N/A | $4.2 \times 10^{-7}$ | N/A | no |

| USE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY[1] General Acute Toxicity |  | MARGIN OF SAFETY[1] Fetotoxicity |  | LIFETIME CANCER PROBABILITY[2] |  |
|---|---|---|---|---|---|---|---|---|
|  |  |  | w/out prot. cloth. | with prot. cloth. | w/out prot. cloth. | with prot. cloth. | w/out prot. cloth | w/prot. cloth. |
| **ABOVE SHOULDER SPRAYS**<br>**AIR BLAST or**<br>**POWER HAND GUN** |  |  |  |  |  |  |  |  |
| ORNAMENTALS (commericals) | Medium | 30-1200 | 6-16 | 42-125 | 12-31 | 81-250 | $7\times10^{-5}$ -<br>$3\times10^{-3}$ | $4\times10^{-7}$ -<br>$9\times10^{-6}$ |
| AVOCADOS | Medium | ND[3] | 4 | 15 | 7 | 31 | $6\times10^{-4}$ | $2\times10^{-6}$ |
| PECANS | Low | 1200 | 4 | 15 | 7 | 31 | $3\times10^{4}$ | $8\times10^{-5}$ |
| LIVESTOCK | Low | 248,000 | >100 | >100 | >100 | >100 | $5\times10^{-6}$ | $1\times10^{-6}$ |
| **ABOVE SHOULDER SPRAYS**<br>**BACK PACK or**<br>**HAND PRESSURE** |  |  |  |  |  |  |  |  |
| ORNAMENTALS (homeowners) | Medium | 75,000 | 47 | >100 | 94 | >100 | $2\times10^{-5}$ | $6\times10^{-6}$ |
| FORESTRY | Low | 1,000 | 18 | 21 | 36 | 42 | $2\times10^{-3}$ | $6\times10^{-4}$ |
| CHRISTMAS TREES (foliar) | High | 10,000** | 2-37 | 9-70 | 4-75 | 16-139 | $4\times10^{-5}$ -<br>$7\times10^{-4}$ | $2\times10^{-5}$<br>$2\times10^{-4}$ |
| **CRAWL SPACE TREATMENTS** |  |  |  |  |  |  |  |  |
| STRUCTURES | Minor if PCP Available |  |  |  |  |  |  |  |
| Applicators |  | 500-1000 | 3 | 18 | 5 | 37 | $4\times10^{-3}$<br>$9\times10^{-3}$ | $1\times10^{-3}$-<br>$3\times10^{-3}$ |
| Residents |  | 10,000 | 3 | N/A[4] | >100 | N/A | $5\times10^{-4}$ | N/A |

* Risk estimates apply to applicators, unless otherwise indicated.
1. Calculated using expected daily exposures.
2. Calculated using expected annual exposures.
3. ND = Not Determined
4. N/A = Not Applicable

## TABLE 7 (Continued)

## USE BY USE SUMMARY OF ESTIMATED PD 2/3 LINDANE RISKS AND BENEFITS*

| SE | BENEFIT | COHORT AT RISK | MARGIN OF SAFETY[1] General Acute Toxicity w/out prot. cloth. | MARGIN OF SAFETY[1] General Acute Toxicity with prot. cloth. | MARGIN OF SAFETY[1] Fetotoxicity w/out prot. cloth. | MARGIN OF SAFETY[1] Fetotoxicity with prot. cloth. | LIFETIME CANCER PROBABILITY[2] w/out prot. cloth | LIFETIME CANCER PROBABILITY[2] w/prot. cloth. |
|---|---|---|---|---|---|---|---|---|
| **USTS** | | | | | | | | |
| SEED TREATMENT | Possibly major except corn | 130,000 | | | | | | |
| Applicators | | | 14 | >100 | 20 | >100 | $8x10^{-5}$ | $5x10^{-6}$ |
| Seed Sowing | | | ND | ND | ND | ND | ND | ND |
| DOG DUSTS | low | | | | | | | |
| Applicators | | N/A | >1000 | N/A | >1000 | N/A | $2x10^{-5}$ | N/A |
| Post-treatment Exposure | | ND | >1000 | N/A | >1000 | N/A | $2x10^{-5}$ | N/A |
| **IELON SHOULDER SPRAYS** | | | | | | | | |
| CUCURBITS | low | 950 | >1000 | >1000 | >1000 | >1000 | $4x10^{-6}$ | $4x10^{-7}$ |
| CHRISTMAS TREES (stump/slash) | high | 10,000 | ND | ND | ND | ND | ND | ND |
| **REPLANT SOIL APPLICATIONS** | | | | | | | | |
| PINEAPPLES | low | 1600 | >1000 | N/A | >1000 | N/A | $10^{-12}$ | N/A |
| **IOUSEHOLD PRODUCTS (OTHER)** | | | | | | | | |
| FLEA COLLARS | low | ND | >1000 | N/A | >1000 | N/A | $2x10^{-4}$ | N/A |
| SHELF PAPER | low | 11,000,000 | >1000 | N/A | >1000 | N/A | $4x10^{-5}$ | N/A |
| HOUSEHOLD SPRAYS | low | | | | | | | |
| Applicators | | ND | >1000 | N/A | >1000 | N/A | $6x10^{-11}$ | N/A |
| Residents | | ND | ND | ND | ND | ND | ND | ND |

USE BY USE SUMMARY OF ESTIMATED PD 2/3 LINDANE RISKS AND BENEFITS* (p. 17)

| SE | BENEFIT | COHORT At Risk | MARGIN OF SAFETY[1] General Acute Toxicity w/out prot. cloth. | with prot. cloth. | MARGIN OF SAFETY[1] Fetotoxicity w/out prot. cloth. | with prot. cloth. | LIFETIME CANCER PROBABILITY[2] w/out prot. cloth | w/prot. cloth. |
|---|---|---|---|---|---|---|---|---|
| IPS | | | | | | | | |
| HARDWOODS | high | 2400 | 11 | 42 | 22 | 83 | $3 \times 10^{-2}$ | $7 \times 10^{-3}$ |
| DOG DIPS | low | | | | | | | |
| Veterinarians | | 130,000 | >1000 | >1000 | >1000 | >1000 | $2 \times 10^{-7}$ | $5 \times 10^{-8}$ |
| Home Applicators | | ND | >1000 | N/A | >1000 | N/A | ND | ND |
| Post-treatment Exposure | | 15,000,000 | >1000 | N/A | >1000 | N/A | $7 \times 10^{-6}$ | N/A |
| DOG SHAMPOOS | low | | | | | | | |
| Applicators | | ND | >1000 | N/A | >1000 | N/A | $4 \times 10^{-5}$ | N/A |
| Post-treatment Exposure | | ND | >1000 | N/A | >1000 | N/A | $2 \times 10^{-6}$ | N/A |
| CLOSED AREA SPRAYS | probably low | | | | | | | |
| MOTH SPRAYS | | | | | | | | |
| Applicators | | ND | >1000 | N/A | >1000 | N/A | $1 \times 10^{-6}$ | N/A |
| Employees | | ND | >100 | N/A | >100 | N/A | $1 \times 10^{-5}$ | N/A |
| FUMIGATION DEVICES | low | ND | >100 | N/A | >100 | N/A | $1 \times 10^{-3}$ | N/A |
| UNINHABITED BUILDING & STORAGE BIN SPRAYS | probably low | ND | 60 | N/A | >100 | N/A | $2 \times 10^{-6}$ | N/A |

## E. Risk-benefit analyses for seven key routes of exposure, and use-by-use final determinations

### 1. Above-shoulder spray applications - air blast or power hand gun equipment

The uses which fall into this category include commercial ornamentals, avocados, pecans, and livestock. Applicators typically use power hand gun equipment for use on ornamentals and livestock. Air blast equipment is used in avocado, pecan, and other types of orchards. Air blast application results in more exposure than power hand gun equipment.

Exposure calculations for these uses show exposure to applicators to be higher than from any other route of exposure to lindane. Even assuming that protective clothing is worn, this high exposure generally results in low margins of safety (MOS) for toxic effects: the estimated MOS for avocado and pecan applicators is 99 and for ornamental applicators is 280; however, livestock applicators have an MOS of 448. Upper-bound cancer risks range from $1.1 \times 10^{-4}$ to $1.7 \times 10^{-5}$ even when protective clothing is worn.

The number of applicators for these uses is in the range of 1-2 thousand, except for the livestock use, which may involve 200-250 thousand.

The benefits of all four air-blast and pressure hand gun uses are high in the sense that cancellation would cause either large or very geographically concentrated economic losses.

Taking all of these considerations into account, the Agency has decided to take the following actions for each of these uses:

#### Commercial Ornamentals:

The risks associated with this use are significant, as with all the air blast uses. Specifically, the potential cancer risk is estimated to be $1.1 \times 10^{-4}$ even if protective clothing is worn. The MOS with protective clothing is 280.

The benefits are high for use on ornamentals, since there are no alternatives for controlling all wood borers on all woody ornamentals. Cancellation would cause major economic losses (approximately $20.6 million) to homeowners and to the woody ornamentals industry, due to borer damage.

Both the risks and the benefits of this use are significant. However, EPA does not believe that cancellation is warranted, since the benefits of this use are so high, the number of applicators potentially at risk (approximately 600) is low, and stringent protective measures (described below) can be used to insure that the benefits exceed the risks.

Protective clothing would not significantly increase costs associated with this use, but would significantly reduce the risks. Therefore, the following protective clothing will be required for applicators: water resistant hat; lightweight protective suit or coveralls; unlined, waterproof (i.e., natural rubber, polyethylene, neoprene etc.) gloves; and unlined, lightweight boots. Mixer-loaders will be required to wear goggles or face shield, waterproof gloves and a waterproof apron. (Risks for mixer-loaders were not calculated separately from applicator risk, but it is known that their exposure is 80-90% higher per unit time. Therefore, EPA believes this requirement is appropriate.)

Since the margin of safety may be less than 100 if protective clothing is not worn, it is important to advise persons who may be at particular risk of the importance of using the clothing indicated. Therefore, EPA will classify this use for restricted use only, thus insuring that this application method could only be used by or under the direct supervision of trained applicators. By preventing untrained or unsupervised applicators from applying lindane with air blast or pressure gun equipment, risks of unacceptably high exposure due to carelessness would be significantly reduced. This restriction will not impose an undue burden since there are already many certified applicators, and training and certification programs are readily available.

Registrants will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category (See 40 CFR 162.10).

Avocados:

Risks associated with the avocado use are also significant. Even if protective clothing (long pants, long-sleeved shirt, waterproof gloves, shoes, hat) is worn, the cancer risk is estimated to be $1.5x10^{-4}$. The MOS for the toxic effects is 99. This margin of safety is considered acceptable for the reversible "general" toxicity, and also affords a sufficient MOS for fetotoxic effects (See C. Margin of Safety Estimates in this Chapter).

There are no registered alternatives for control of mirids on avocados. The benefits of this use are very high in Florida; cancellation there would cause major economic losses (approximately $8.7 million in producer losses due to downgrading and fruit loss). However, the impact of cancellation would be negligible outside of Florida - although avocados are grown in other states, the target pests (mirids) are not currently a problem outside of Florida.

The risk-benefit balance for this use is again a difficult one, since both the risks and benefits are significant. In EPA's judgment, cancellation

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is not warranted since less stringent measures could reduce the risk levels, since the benefits are high (there are no suitable alternatives for control of mirids), and since cancellation would have a major deleterious impact on the Florida avocado industry.

EPA extensively investigated various ways to reduce the risks associated with this use. It does not appear feasible to alter the application equipment (air blast), reduce the active ingredient concentration, or apply lindane less frequently.

In conclusion, although the risks cannot be eliminated, stringent protective measures will reduce them enough so that the benefits (which are high) will exceed the risks. Therefore, EPA will retain lindane's use on avocados, but will impose stringent protective measures. These include:

- Requiring the same protective work clothing for applicators and mixer/loaders as stipulated for commercial ornamentals:
- Restricting the use to certified applicators;
- Requiring label updates, to include proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate to the product's toxicity category.

**Pecans:**

Risks associated with lindane use on pecans are similar to the risks described above for avocados. Even with protective clothing, the upper-limit cancer risk is estimated at $7.5 \times 10^{-5}$. The MOS for general, liver, and fetal toxicity is 99.

Economic losses if lindane were not available would total approximately $1.5 million annually, due to a combination of increased control costs and crop losses. There are alternatives for controlling pecan phylloxera, however, these alternatives also have potential risks associated with them and are subject to the same high-exposure application method as lindane. Endosulfan, lindane's major alternative, is in a higher toxicity category than lindane and is usually applied twice as often. Also, there are serious uncertainties regarding its environmental effects and its potential to cause kidney damage.

Other pesticides (malathion, oils) are registered for this use, but they are not as effective and require more frequent application.

Approximately 1,200 applicators are estimated to be involved in the pecan use.

Since cancelling this use might promote the use of a pesticide with potentially higher risks, since other alternatives are less effective, and since the benefits exceed the risks if appropriate measures are taken, cancellation of the registrations for pecan use is not warranted.

EPA explored many options other than cancellation. Measures such as different application equipment, lower concentrations, and fewer applications are either impractical, or would not significantly reduce the risk. The only viable option is to require protective clothing for applicators, which is reasonable in this case since lindane is applied to pecans in early Spring.

Considering the above points, EPA will take the following steps to insure the benefits of lindane's pecan use exceed the risks:

- Classify lindane pecan products for restricted use;
- Require the same protective clothing as with commercial ornamentals use.
- Require label updates, including descriptions of proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warnings appropriate for the product's toxicity category.

### Livestock

Lindane livestock uses may be divided into two primary application categories: livestock dips and sprays. Applicator exposure from the dips is insignificant compared to exposure during spray operations. Also, a pharmaceutical product, which controls mites and ticks, is currently in the final stages of development. If approved, this product could soon make lindane dips (but not sprays) obsolete. For these two reasons, we have considered livestock sprays separately from the dips for risk and regulatory analysis.

The following discussion applies only to livestock sprays. Other lindane products for treating livestock will be regulated similarly to products which share their exposure potential. For example, livestock dips will be subject to applicable requirements from the dips category (see Chapt. VIII, D.), and topical gels will be subject to requirements similar to other uses where the applicator comes directly into contact with the material, such as lindane shampoos, also see Chapter VIII, D.

Assuming that long-sleeved shirts, long pants, and waterproof gloves are worn, the cancer risk associated with livestock sprays is estimated to be $1.7 \times 10^{-5}$. The MOS for general toxicity is 448.

The economic losses if lindane were not available for this use would be moderate. However, one of lindane's most important uses is for scabies control. Alternatives exist for livestock use, but with the exception of toxaphene, are less effective (EPA 1982c).

The risks and benefits of this use are both significant. However, EPA believes that if appropriate measures to reduce the risks are taken, the benefits outweigh the risks and cancellation is not warranted.

EPA examined many options for reducing the risk without cancelling these uses. The concentration of lindane would have to be reduced a great deal to result in a significant improvement in the risk estimates, and other application methods are not currently feasible. Hence, none of these options provides a way to reduce the exposure without seriously compromising either efficacy or practicality.

Considering the combination of fairly high risks and benefits from livestock uses of lindane, EPA will require all reasonable restrictive actions short of cancellation. This will insure that the benefits of this use exceed the risks. Measures which will be required include:

- Protective clothing requirements for applicators and mixer/loaders are the same as for commercial ornamentals;
- Restricted use classification (since the Agency anticipates that persons trained in the risks of pesticide application are more likely to read the labels and to take the required precautions).

Registrants will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### 2. Above-shoulder sprays - backpack or hand-pressure equipment

The uses which fall into this category include forestry, foliar treatment of Christmas trees, and homeowner ornamentals. Back-pack sprayers are used for forestry and Christmas tree uses, while hand-pressure equipment is typically used for non-professional application to ornamentals.

Exposure levels associated with this use category are higher than most uses, but not as high as those for which air blast equipment is used. Assuming protective clothing is worn, the margins of safety are all greater than 500, and the cancer risks are approximately $1.9 \times 10^{-6}$ for ornamentals, $1.2 \times 10^{-5}$ for Christmas trees, and $1.2 \times 10^{-4}$ for forestry.

The number of people who would be exposed to these risks is high for homeowner ornamentals (estimated at 75,000), medium for Christmas trees (10,000) and low for forestry (1000).

Potentially high economic losses would occur if any of the three uses in this category were cancelled, since alternatives are not available for control of wood borers. Although economic impacts to the affected industries and the public could not be quantified, the impacts would be minor in cooler climates where cultural, non-chemical control measures are practiced. Southern forest owners would be hard-hit economically, since they rely heavily on chemical control. Homeowners in many areas could suffer aesthetic and economic losses in forested areas.

Taking all of these considerations into account, EPA will take the following actions for each of these uses:

Forestry:

Cancellation of the forestry use is not warranted, since the benefits are high and the risks can be sufficiently reduced by other mechanisms, such that the benefits will exceed the risks.

The Agency believes that although the cancer risk is an upper-bound, ($1.2 \times 10^{-4}$) it is prudent to restrict the use and to require protective clothing. These measures would not significantly increase costs associated with forestry uses, but would decrease the possible cancer risks. Applicators and mixer/loaders will be required to use the same protective clothing as with commercial ornamentals.

In addition, registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

Homeowner Ornamentals:

Cancellation of this use is not warranted since the benefits are high and the benefits will exceed the risks if less stringent measures are taken.

The absolute risk levels from this use are the lowest in the foliar application use group, but the number of persons who might be exposed to these risks is high and is of concern to the Agency.

A protective clothing requirement would not increase the costs of this use significantly, but would significantly reduce the possible cancer risk. Therefore, the following protective clothing is prudent and will be required for applicators: long-sleeved shirt, long pants, waterproof gloves, full foot covering, and a head covering such as a hat.

Although the Scientific Advisory Panel recommended restricting this use to certified applicators, EPA has considered this carefully and does not believe it is reasonable or necessary, for the following reasons: 1) The Agency's revised estimate of oncogenic risk is $1.9 \times 10^{-6}$. The revised MOS is more than 3500. In the PD 2/3 the risk estimate was $2.5 \times 10^{-5}$ and the MOS over 100. (The difference is due to estimating exposure based on a final use concentration of 0.06% as prescribed by the existing labels versus the 0.5% assumed in PD 2/3) 2) The requirements are easy for homeowners to follow. 3) The benefits of the use would be significantly reduced by such a requirement, since pest control firms are often unwilling to take jobs that do not include care of an entire lot. Thus, even though the homeowner's pest problems may be limited to one or a few trees, the cost to a homeowner of obtaining a professional applicator's services could be unnecessarily high. 4) Restricting the use to certified applicators could result in higher total use of lindane, since professionals often use power hand gun equipment rather than backpack or hand-pressure equipment. Therefore, the use will not be restricted to use by certified applicators.

Registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### Christmas Trees (foliar application):

Cancellation is not warranted, however, the risks are of concern and can be mitigated by less stringent measures. In addition, the benefits of this use are high, due to the lack of alternatives for some of the critical pests.

However, protective clothing will be required as stipulated for commercial ornamentals and the use will be restricted to certified applicators.

Registrants will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### 3. Structural Treatments

The only use which currently falls into this category is structural use for treatment of wood borers, powder post beetles, and subterranean termites. This use of lindane has very high benefits since there are no comparable alternatives available for this use pattern.

Protective clothing is routinely worn by applicators during structural application of lindane. Approximately 8,000 persons apply lindane in structures.

EPA will not cancel this use since the benefits are so high and since protective clothing, which applicators usually wear, keeps the risks at an acceptable level. For applicators, the MOS is 5435 when protective clothing is worn. The cancer risk is estimated to be $7.4\times10^{-6}$ while the number of applicators exposed is approximately 8,000.

Since a requirement to wear protective clothing would insure that the risks remain at acceptable levels, would not negatively affect the benefits, and is consistent with current use practices, the Agency will require that applicators wear protective clothing as described under commercial ornamentals. In addition, respirators (approved by OSHA regulation 29 CFR 1910.134) will be required for applicators working in enclosed areas such as crawl spaces.

In addition, registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category. Although it is expected that the use will tend to limit itself to professionals for practical reasons, EPA will restrict this use to certified applicators, because of the importance of correctly identifying the species of wood infesting beetle prior to treatment, the specific control measures needed to be undertaken, and the fact that occupants can be exposed to treated areas.

Post-treatment exposure levels are low enough that the Agency feels no actions are required to reduce them. The estimated margin of safety is 7246. The upper-limit cancer estimate is $3\times10^{-6}$.

### 4. Dip Applications

The uses which fall into this category include hardwood logs, dog dips, and dog shampoos. Although all may be considered dip applications in that the treatment involves immersion into a liquid formulation, the actual mechanism of immersion differs between these uses and affects the levels of exposure associated with each (EPA 1982b).

In general, these uses involve higher exposure to applicators than other application methods except for the above-shoulder sprays. Unlike most of the other use groups, however, exposures differ markedly between the uses within this group. Some involve exposure to homeowners, possibly including children, while others are industrial uses. Thus, the exposure and risk estimates, as well as the relevant regulatory considerations, must be considered individually.

EPA will require special disposal instructions for lindane dips used in large quantities, such as the hardwood and livestock uses. However, smaller quantities such as are used for dog dips in veterinary establishments will not be subject to these requirements.

### Hardwood Logs and Lumber:

For this use, EPA estimated risk under the assumption that protective clothing is worn. Actual monitoring has shown that long-sleeved shirts, long pants, rubber aprons, waterproof gloves and hard hats are routinely used (EPA 1982b). Estimates show the MOS to be greater than 1000 and the upper-bound cancer risk to be around $4x10^{-4}$ with these protective clothing measures.

Approximately 840 people are estimated to be exposed. The cancer risk is about $3.6x10^{-4}$. The MOS for this use is 3846, which is very adequate.

The economic benefits of this use are high. The approximate cost if lindane were cancelled and no alternative were available would be $240 million annually. However, a more reasonable estimate of expected losses is $500 thousand annually; this estimate is based on the assumption that endosulfan, an alternative to lindane, would be available and equally effective.

Cancellation is not warranted since the benefits of this use are significant, the number of applicators at risk is low, and the primary alternative (endosulfan) has potentially equal or greater risks associated with it (please refer to discussion of endosulfan as an alternative for the pecan use in Section VI., E., 1.).

Protective clothing keeps the risks adequately low in relation to the high benefits. It would not significantly increase the costs of this use, is already routinely used by most of the industry, and is a prudent measure for a use which involves exposure to potentially large quantities of lindane. Therefore, protective clothing will be required for persons in areas where splashing, or handling of wet wood, is expected. The clothing is described under commercial ornamentals. Hard hats are not considered necessary as a safety requirement for protection against lindane, although EPA recognizes that they are often worn for other reasons.

Registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

It would not be useful to restrict this use to certified pesticide applicators, because the applicators are not significantly exposed. Rather, the workers in the area of lindane dip are most exposed and are therefore the ones needing protection through protective clothing, as required above.

Dog Dips:

EPA prepared estimates of risk from dog dips for three groups: veterinarians, home applicators, and those who are exposed to the dog "post-treatment".

Risks associated with post-treatment exposure are acceptably low. Without protective clothing, the MOS for general toxicity and fetal effects is greater than 58000. The estimated upper-bound cancer risk is $4.2 \times 10^{-7}$. Also, there is not a significant risk to applicators of general, fetal, and liver toxicity, since the MOS is well over 8000 with or without protective clothing. Therefore, for regulatory purposes, EPA is only concerned about the possible cancer risk to people who are exposed during application.

EPA's estimates of the cancer risk to veterinarians assumes that they would treat approximately 26 dogs per year with lindane dips. Under this assumption, the upper-bound cancer risk is estimated to be $4.2 \times 10^{-6}$ if protective clothing is worn. Protective clothing in this case is assumed to include long-sleeved work shirt, long pants, elbow length waterproof gloves, and an waterproof apron. Approximately 130,000 veterinarians (and their assistants) are expected to treat dogs with lindane dips each year.

The possible cancer risk to home applicators of lindane dog dips were not calculated separately. However, the Agency assumes that the risks to home applicators are not a significant concern, since they would be exposed to far fewer applications than veterinarians (perhaps 1-2 times per year, as opposed to the estimated 26 times per year for veterinarians).

One additional consideration, unique to this use, is the problem of acute toxicity to domestic animals. Seven dog deaths were reported between 1966 and 1978 resulting from use of these dog washes, but the Agency assumes that the number of actual deaths is higher than the number of reported deaths. In addition, at least nine dogs were reported to have been made very sick as a result of treatment with the dips during the same period. Whether lindane alone is the cause is difficult to establish, because the dips are usually formulated with other chemicals as well. However, the case histories show that dog deaths usually resulted from misuse or carelessness, such as not diluting the dip sufficiently. When dogs are treated with dips for scabies, they are often quite ill to begin with; it is probably to be expected that a certain number would die as a result of a combination of their poor health and exposure to the dip.

Therefore, all labels will be required to include a statement warning that "improper dilution of this product could cause serious injury to your pet".

The benefits of this use are very high for that proportion which is used to treat scabies, because there are no equally effective alternatives for that use. Against other pests such as ticks and fleas the use has low benefits, (that is, cancellation would not cause significant economic losses) since there are numerous alternatives in the same price range as lindane.

Taking these factors into consideration, EPA believes the following actions for dog dip uses of lindane will insure that the benefits exceed the risks of this use.

Cancellation of the dog dip for control of scabies (which is caused by mites) is not warranted, considering the high benefits. The cancer risks to veterinarians can also be significantly reduced with the use of simple protective clothing measures. Therefore, the following protective clothing will be required for veterinarians: elbow-length waterproof gloves, a waterproof apron, and unlined, waterproof boots.

Use of dog dips to control pests other than mites, such as fleas and ticks, will be cancelled because of the low benefits of this use (i.e., availability of registered alternatives) and because of the cancer risk to applicators. To prevent use for pests other than mites, labels will specify, "for treatment only of mites; treatment of other pests is prohibited."

Registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning and practical treatment in the event of poisoning (for both the applicator and the dog), and warning statements appropriate for the product's toxicity category.

Although the Scientific Advisory Panel suggested restricting these products to certified applicators and veterinarians, EPA does not believe these measures are necessary. The reasons are that the MOS for general and fetal toxicity are more than adequate, and the cancer risk to home applicators should also be minor, since home applicators are expected to use these products significantly less often, over a lifetime, than veterinarians. (Readers who wish to examine the exposure assumptions which lead to these risk estimates will find them in Appendix III.)

As with all lindane products which are available to the general public, the Agency is concerned about misuse by children. These products will therefore be required to promptly comply with the EPA child resistant packaging regulations, which require child resistant packaging in those cases where the active ingredient concentration is greater than 6.5% (46 FR 15104). For the same reason, labels must include a statement that "children should not be allowed to apply or handle this product."

Dog Shampoos:

EPA prepared estimates of exposure and risk from use of lindane dog shampoos

Risks from post-treatment exposure are sufficiently low (see Table 6) that the Agency believes no action is necessary to further reduce them. Although the margin of safety for applicators is well over 1000, and therefore more than adequate, the estimated upper-bound cancer risk is high for a household use. Specifically, the upper-bound cancer risk for home applicators is estimated at $2.2\times10^{-5}$, assuming use of one to twelve times per year. The Agency believes that this risk is especially significant when compared to the benefits of this use, which are negligible since there are many alternative flea shampoos available in the same price range as lindane shampoos.

The Agency was unable to estimate the number of persons who would be exposed to these risks. However, data from a 1977 survey by Hooker Chemicals showed 16,700 "units" of lindane pet shampoos sold in that year (Correspondence, 1982b). This may be taken as a reasonable estimate of the maximum number of applicators exposed (assuming each unit was sold to a different person). The types of persons exposed would mostly be the general public (including children) and some veterinarians.

Having considered the preceding factors, the Agency has decided to take the following actions regarding lindane dog shampoos:

Cancellation does not seem to be warranted since the risks could be mitigated. by less stringent measures. EPA therefore considered a number of other ways to reduce the risk, but most were impractical. Altering the product concentration would make almost no impact on the exposure estimates, since we are already assuming a ten-fold dilution with water when the shampoo is in use. Protective clothing requirements are not considered reasonable for homeowners, since waterproof gloves and aprons are not readily available, and could not be expected to be worn by the average home applicator. EPA also considered limiting the number of times the shampoos can be used, as a way of reducing the cancer risk. However, to reduce the risk to an acceptable level, applications would have to be limited to less than once annually. This is clearly impractical. Label warnings were considered, but do not sufficiently alleviate the concern that children may misuse the product, since they are less likely to understand and follow directions regarding proper dosages.

Taking all of these considerations into account, EPA finds it necessary to restrict the use of lindane shampoos to certified applicators (veterinarians would not be precluded from using these products under this requirement; see section 171.4(e) of the EPA Applicator Certification Regulations). The Agency believes that this requirement is necessary even though other dog products reviewed (dips) do not require this restriction. This is primarily because if the upper-bound cancer risk estimated for shampoos is correct, it is unacceptably high when compared with the almost negligible benefits of this use. Furthermore, as explained above, EPA cannot reduce the risk by other means. The other dog products do not entail such high risks (see Table 6) and therefore need not be subject to the same measures (see Appendix III for an explanation of the exposure assumptions leading to these risk estimates).

EPA will require applicators to wear protective clothing, including waterproof gloves and aprons. Such clothing will reduce the upper-bound cancer risk to $4.5\times10^{-6}$. The protective clothing requirement could be easily met by those allowed to buy and use lindane shampoos, since veterinarians usually have waterproof gloves and aprons.

Registrants of dog shampoos will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning and practical treatment in the event of poisoning (for the dog and the applicator), and other warning statements appropriate for the product's toxicity category.

### 5. Enclosed Area Sprays:

The fact that respiratory exposure is the main route of exposure distinguishes enclosed area sprays from other lindane uses.

Exposure and risk to applicators are lower than the previous use groups discussed (overhead sprays, crawl space treatments, and dips). The margins of safety are more than adequate: approxiamtely 3000 or more even if protective clothing is not worn. Upper-bound cancer risks (again assuming no protective clothing) range from a high of $9.2 \times 10^{-4}$ for fumigation devices, to a low of $1.5 \times 10^{-6}$ for uninhabited building and storage bin sprays.

There are numerous alternatives available for all of the enclosed-area spray uses. Their benefits are estimated to be rather low.

Approximately 840 people apply lindane in uninhabited buildings and storage bins. The Agency was unable to obtain estimates of the number of persons who apply moth sprays or use fumigation devices.

Taking all of these considerations into account, the Agency has decided to take the following actions for these uses:

### Moth Sprays:

The benefits of this use are low, and the risks are not unacceptable. Specifically the margin of safety for general toxicity is greater than 3000, whether or not protective clothing is worn. The maximum cancer risk is estimated at $5.6 \times 10^{-5}$ without protective clothing, and $5 \times 10^{-5}$ with protective clothing. These estimates do not assume the use of respirators even though respiratory exposure is the most significant route in this case. Use of a respirator would reduce respiratory risk by a factor of 10. This is why the risk estimates assuming protective clothing is worn (excluding a respirator) are not significantly different from those when protective clothing is not worn. Roughly 1000-3000 persons are exposed annually to lindane moth sprays.

Risks to employees following moth spray treatments are not of sufficient concern to warrant protective measures, especially since most dry cleaning establishments have strict ventilation requirements which would be expec

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to aid in dispersing any lindane vapors which may be present. Also, the National Institutes of Occupational Safety and Health (NIOSH) have established allowable air levels for lindane in dry cleaning establishments, which are sufficient without further action by EPA.

In conclusion, the benefits of moth spray products are low, but the risks to applicators are not unreasonable and cancellation is not warranted.

Although EPA acknowledges that protective measures may not be necessary if the cancer risk is significantly lower than estimated, the potential cancer risk can be easily and inexpensively reduced to a more acceptable level by decreasing the respiratory exposure. Therefore, EPA will require applicators to wear MSHA/OSHA-approved cartridge respirators during application of lindane moth sprays.

Also, registrants will be required to update their product labels to meet current standards. Labels must state that this product should only be used in a well-ventilated area. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### Fumigation Devices:

This use entails no significant risk to homeowners of causing general, fetal, or liver effects. The cancer risk to homeowners associated with the indoor use of these devices is $9.2x10^{-4}$.

The benefits of these uses are negligible, since there are numerous alternative products which kill the same spectrum of insects.

The Agency was not able to estimate the number of people exposed to these products, but fumigation devices are available to the general public.

EPA made many attempts to consider ways of reducing the risks associated with this product, and invited suggestions from the registrant. However, the risks associated with these products are based on data submitted by the registrant and on reasonable assumptions of ventilation (Memo, 1982i). The potential cancer risk associated with the indoor use of smoke fumigation devices is unacceptable. Therefore, the Agency will cancel the indoor use of smoke fumigation devices.

### Uninhabited Building and Storage Bin Sprays:

The benefits of this use are low but the risks are also low. Specifically, applicators' maximum risk of cancer is $1.5 \times 10^{-6}$ if protective clothing is not worn, and $6.4 \times 10^{-7}$ if it is worn. Margins of safety for acute and fetal effects are greater than 50,000 with or without protective clothing.

The Agency was unable to obtain estimates of the number of people who could be exposed to lindane through this use.

Taking the above into consideration, the Agency believes the risks of these uses are not unreasonable, so there is no justification for cancelling or restricting them.

Registrants of these uses will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

## 6. Dusts

Uses which fall into this category include planter box seed treatment, and dog dusts. Exposure and risks from these uses are lower than those associated with the use groups previously discussed, namely above-shoulder sprays, dips, and enclosed area sprays.

Post-treatment exposure estimates were calculated for persons sowing treated seed or being exposed to dogs that have been treated with lindane dust. Risks from post-treatment exposure are sufficiently low that the Agency does not consider it necessary to take action to reduce them.

Specific considerations relevant to applicator risks from the dust uses of lindane are discussed below.

### Seed Treatment:

Applicator risks from this use are moderately low. The margin of safety for toxic effects is 5000 if protective clothing is worn. The cancer risk is $3 \times 10^{-6}$ if protective clothing is worn. The number of applicators potentially exposed to these risks is estimated at about 130,000.

EPA does not consider it reasonable to cancel this use since the risks are relatively low and the benefits, although unquantifiable, have been attested to as significant by numerous users.

The Agency acknowledges that the cancer estimates are conservative, and that if the risks are actually lower than estimated they may not be unreasonable. However, protective clothing is a prudent and inexpensive measure which would reduce the risks associated with this use without adversely affecting the benefits, and would insure that the risks are outweighed by the benefits. Therefore, the Agency will require the following protective clothing during manual seed treatment operations: long sleeved shirt, long pants, gloves, and a disposable paper dust mask covering at least one-third of the face. However, no protective clothing will be required during automated seed treatment operations, closed-system seed treatment, or seed sowing, since exposure associated with these activities is negligible.

The Agency will also require, for commercial dust uses, the following precaution on the label: "This product should be applied in a well-ventilated area".

All registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

The Agency does not consider that the risks associated with this use are substantial enough to justify restricting the use to certified applicators.

### Dog Dusts:

Applicator risks of general toxicity and fetal effects are low: the margin of safety for toxic effects is greater than 2500 without protective clothing. The upper-bound cancer estimate is $6.4 \times 10^{-6}$ if protective clothing is not worn. This is reduced to $1.4 \times 10^{-6}$ if protective clothing is worn. The number of persons potentially exposed to these risks could not be estimated, but the products are available for use by the general public.

The FIFRA Scientific Advisory Panel recommended cancelling these products. The Agency does not believe cancellation is necessary, since less stringent measures would reduce these risks enough to insure that they are not unreasonable, and would not adversely affect the benefits of the use. However, the Agency is concerned that children may be excessively exposed either due to misuse or mishandling of a household pesticide product, or via the contact with treated pets. Since there are alternatives to this use pattern and since the benefits are low, the Agency will restrict this use to certified applicators. As with dog shampoos, veterinarians would not be precluded from using lindane dog dust products (see Section 171.4(e) of the EPA Applicator Certification Regulations).

In addition, the Agency will require the following label recommendation: "this product should be applied in well-ventilated areas".

Registrants will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### 7. Below-Shoulder Sprays

This use group includes cucurbits, and the stump/slash treatment of Christmas trees. Risks from these uses tend to be lower than from the use groups previously discussed.

#### Cucurbits:

The risks from this use are very low. The margins of safety for toxic effects are greater than 28,000. The upper-bound cancer risk is $3.7 \times 10^{-7}$ without protective clothing and $1.9 \times 10^{-7}$, if protective clothing is worn. The estimated number of people exposed to these risks is about 950.

Since these risks are not unreasonable, the Agency does not intend to cancel or restrict these products except that registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

#### Christmas Trees (stump/slash application)

The estimated general toxicological risks from this use are also low, and are clearly exceeded by the benefits if appropriate measures are taken. The margin of safety is greater than 250 with protective clothing. The maximum cancer risk is $3 \times 10^{-5}$ with protective clothing. Approximately 10,000 applicators are exposed.

The cancer risk from this use is not acceptable to the Agency. However, the Agency believes this to be a valuable use of lindane. Therefore, cancellation is not recommended; however, this use will be restricted to application only by certified applicators. In addition, protective clothing will be required as described under commercial ornamentals.

Registrants will be required to update their product labels for this use, to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### 8. Pre-Plant Soil Applications

The only currently registered use which falls into this category and was reviewed by the Agency is pineapples. The sugarcane use (currently used only under the Section 18 emergency use provisions) was not separately reviewed, but is expected to involve similar exposure to the use on pineapples and will therefore be subject to the same requirements.

#### Pineapples

Pre-plant soil applications in general involve very low exposure to applicators. Even if no protective clothing is worn, the margin of safety for toxic effects is greater than 1,000,000. The maximum cancer risk is $1.5\times10^{-11}$. These risks are negligible both in absolute terms and relative to the benefits. Therefore, the Agency does not intend to cancel or restrict this use. However, registrants will be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category.

### 9. Other Household Products

The uses which fall into this category are flea collars, shelf paper, and household sprays. All of these uses have low benefits, but also low risks. Specifically, the margins of safety for toxic effects are all greater than 1000. The highest cancer risk estimated for any of these products is $4.9\times10^{-6}$ for the household spray applicators. Specific estimates for the other uses may be found in Table 6.

EPA attempted to estimate whether cumulative exposure to lindane household products might be a significant concern. Although no quantitative estimate could be developed, EPA believes the likelihood of significant cumulative exposure is remote. Lindane holds such a small portion of the household pesticide market (less than 3%) that it is unlikely that a household would purchase two lindane products for different uses. Also, the season or site of application would be likely to differ. (Savage et al., 1979; Correspondence, 1982a).

The FIFRA Scientific Advisory Panel and the U.S. Department of Agriculture recommended cancelling these uses. However, EPA does not currently believe there is now sufficient justification for cancellation. The highly conservative estimates of risk noted in PD 2/3 were $2\times10^{-4}$ (flea collars) and $4\times10^{-5}$(shelf paper). The corrected estimates of risk are $4.2\times10^{-6}$ and $2.1\times10^{-6}$ respectively.*

Considering these risks, the Agency believes there is justification only for minor restrictions on lindane household products. These include the restriction that children should not be allowed to handle or use the products, and that children and pets should not be allowed in treated areas until surfaces are dry. Statements to this effect will be required on all lindane household products.

All registrants will also be required to update their product labels to meet current standards. Labels must describe proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category. In the case of household products, this will specifically include the following label statement: "Do not allow children to apply or handle this product".

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* Lindane floor wax uses have been voluntarily withdrawn from the market and were therefore not considered in this analysis.

## E. Summary Conclusion On Dietary Risk

There are a number of tolerances for lindane (40 CFR 180.133) ranging from 0.01 ppm (pecans) to 7 ppm in fat of meat animals. Using the conventional method of total maximum residue contribution (TMRC) calculation a 0.78 mg/day intake can be computed. In addition, there are several action levels established for lindane including 0.3ppm in milk fat. Both PD 2/3 and PD 4, however, have used figures derived from FDA Total Diet Composites, collected over several years, to estimate dietary exposure. In the PD-4 the Agency now estimates the dietary exposure to be between 0.3 and $1.6x10^{-5}$ mg/kg/day. The estimated cancer risk assessment for these exposure figures range from $3.3x10^{-6}$ to $1.7x10^{-5}$, depending on whether all the market basket data are considered or only those of the last several years.

The Agency does not consider these risks unacceptable for the following reasons: (1) because of the uncertainty about lindane's oncogenic potential as a human oncogen as discussed in this PD (Section II. A.2), (2) because residues on food seem to be declining as shown by the market basket survey, and (3) because the Agency used a conservative model for estimating risk which produced figures representing the upper bounds of the estimated risks. Moreover, the Agency has good reason to believe that lindane residues, if any, on food are not necessarily a result of direct agricultural applications to a particular crop. Thus, cancellation of agricultural uses would not likely eliminate residues on food items. To resolve this issue, the Agency will place special emphasis on the reevaluation of tolerances and action levels presently in effect. These reevaluations will take place during the Agency's Registration Standard program for lindane. At that time, the Agency will again assess the dietary exposure and the actual sources of lindane in the food supply. At that time it will consider any further regulatory action that might be necessary to reduce dietary exposure and risk.

EPA also realizes that residue levels for lindane at or about tolerance levels, i.e., exposures commensurate with TMRC, would not be considered an acceptable risk, and that dietary exposure should not exceed about $1.6x10^{-5}$ mg/kg/day. It therefore follows that monitoring the food supply for samples which exceed established tolerances (as is the case for most pesticides) is not in itself sufficient in the case of lindane. EPA will, therefore, evaluate FDA's and USDA's data on regulatory compliance samples as well as the Total Diet Composite samples. This will further serve to assure the Agency that the assumptions made with respect to lindane's presence in food are essentially correct and that dietary exposure will not substantially increase. In addition this continuing surveillance data will be used in re-evaluating the tolerances and action levels.

## F. Risk/Benefit Considerations Which Apply To All Lindane Products

Besides the use-specific risks and benefits discussed in the preceeding section, the Agency has concerns which apply to all lindane products. These considerations are discussed in this section.

### 1. Possibility of Accidental Misuse

First, the Agency is concerned about general misuse of lindane, although some acute effects are irreversible effects are more serious at high levels of exposure (convulsions and death can result). Because misuse has resulted in high levels of exposure and serious adverse effects in the past, the Agency feels that all lindane products should be required to meet certain basic labeling standards which would mitigate the chance of misuse by informing consumers and applicators of how to properly use lindane products. Labeling improvements are a particularly desirable type of requirement since they will not adversely affect the benefits of the continued use of these products.

Therefore, all household products must include the following statement: "Do not allow children to handle or apply this pesticide product". Also, all registrants will also be required to include information on the label regarding proper handling and disposal, symptoms of poisoning, practical treatment in the event of poisoning, and other warning statements appropriate for the product's toxicity category. All labels must disclose all active ingredients and the percentages in which they occur.

### 2. Possibility of Aquatic Contamination

Although EPA is not aware of current problems with lindane contaminating aquatic environments, the potential exists, if lindane were to get into such environments through routine practices. Therefore, EPA will prohibit aerial application of lindane, as suggested by the U.S. Department of Agriculture, since it could result in significant runoff and drift. EPA will also deny any future requests to register lindane for direct application to aquatic environments.

## G. Voluntary Actions To Which Registrants Of Technical Lindane Have Agreed: Mutagenicity Testing

The Agency has determined that there is an outstanding and important question of whether lindane is a mutagen, and believes that the lindane mutagenicity data base should be completed. In addition, further information about lindane's mutagenicity may explain whether lindane acts through a genotoxic carcinogenic mechanism.

In order to accomplish the development of additional mutagenicity data on lindane, an informal, voluntary agreement has been reached with the registrants of technical lindane represented by CIEL. The Agency will issue a letter pursuant to section 3(c)(2)(B) of FIFRA to all registrants of lindane indicating that additional mutagenicity data are required. The voluntary agreement will likely satisfy the provisions of 3(c)(2)(B) for joint development of data. The short term tests which CIEL has agreed to sponsor are as follows: (i to iii).

### i. In Vitro Gene Mutation Testing in Mammalian Cells

This type of assay was agreed upon because the only validated test types are those conducted in bacterial cells. Although there are potential problems with the exogenous activation for such *in vitro* assays, the lack of a comprehensive, validated series of tests by the more insensitive *in vivo* approach leaves *in vitro* testing in mammalian cells as the only option. (It is also more rapid, more sensitive, and less costly). One purpose of this test is to answer questions about lindane's metabolic activation; specifically, modulation of secondary enzyme activity in mammalian systems, if feasible. Exogenous activation from the CFI mouse strain will be employed. If valid positive results are found in *in vitro* tests, one then may pursue more productive lines *in vivo*, depending on the particular effects generated.

### ii. In Vivo, Oral and Parenteral Assay for Sister Chromatid Exchange

This testing is important in or[illegible] to answer questions about lindane's activation outside the liver, coincident wi[illegible]s unresolved chromosomal effects. Comparison of oral vs. parenter[illegible]istration of the test compound could help resolve the issue of "anaer[illegible]tabolites potentially active in oncogenesis and/or mutagenesis.

### iii. In Vitro Test in Mammalian Cells Under Anaerobic Conditions

The purpose of this assay would be to shed light on the differences between *in vitro* and *in vivo* conditions.

Because this type of assay is not standardized at this time, its completion will depend on whether or not an adequate test protocol can be agreed upon by EPA and CIEL.

### iv. Other Tests

Other tests which have been recommended to CIEL for completion would also help to fill data gaps in the current mutagenicity data base. However, since these are not necessary for the primary goal of completing the RPAR, CIEL will be completing these tests over a period of several years as a secondary priority to the tests discussed above.

The following tests are those recommended as a second priority:

- Micronucleus Test _in vivo_;
- Sister chromatid Exchange _in vitro_, using CHO cells, or any other cell type with a growing data base;
- Stimulation of Hepatic Pre-Neoplastic Foci:
- Unscheduled DNA Synthesis (DNA-repair) test in rodent hepatocytes (HPC-UDS).

## VIII SUMMARY OF REGULATORY POSITION

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## A. Requirements for Above-Shoulder Sprays: AIR-BLAST OR POWER-HAND-GUN

1. ALL air-blast and power-hand-gun uses will be subject to the following requirements:

   - Restriction to use by certified applicators only
   - Protective clothing will be required for (See VII E. 1. Commercial ornamentals).
   - Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses).

2. USE-SPECIFIC requirements for air-blast and power-hand-gun uses are as follows:

   Ornamentals:

   - Restriction of use (commercial application) to certified applicators.
   - Protective clothing required.

   Avocados:

   - Restricted to use by certified applicators only.
   - Protective measures required for applicators (See VII E. 1. Commercial ornamentals)

   Pecans:

   - Restricted to use by certified applicators only
   - Protective clothing required for applicators (See VII E. 1. Commercial Ornamentals)

   Livestock:

   - Restriction of use to certified applicators only
   - Protective clothing required (see VII E. I. Commercial ornamentals)

   Other Uses:

   - Protective clothing for other air blast or power hand gun uses must be similar to that for the specific uses described here. Specifically: waterproof clothing or roof-type shelters will be required unless EPA's Registration Division determines that it is infeasible for the particular use. At a minimum, long-sleeved shirt, long pants, waterproof gloves, full foot covering, and appropriate accessories for the type of use will be required.

## B. Requirements for Above-Shoulder Sprays: Backpack or Hand Pressure Equipment

All uses:

- Protective clothing required for applicators: long-sleeved shirts, long pants, impermeable gloves, full foot covering, and head covering such as hat or bandana.
- Protective clothing required (see VII. E. 1. commercial ornamentals).
- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses").
- Forestry use restricted to certified applicators.

## C. Requirements for Structural Uses

- Use restricted to certified applicators.
- Protective clothing required (See VII. E. 1. Commercial ornamentals).
- MSHA/OSHA-approved respirators for applications in enclosed areas such as crawl spaces.
- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses").

## D. Requirements for Dip Applications

- Special disposal instructions will be required for lindane dips used in large quantities.
- For all lindane dip uses, labels must be updated as described (see "Requirements for All Uses") in Chapter VIII, J.

Hardwoods:

- Persons working in areas where splashing or handling of wet wood is expected, are required to wear protective clothing as described in VII. E. 1. Commercial ornamentals

Dog Dips:

- Protective clothing required for applicators: long-sleeved shirts, long pants, elbow length impermeable gloves, and waterproof aprons;
- Labels must include following statement: "Improper dilution of this pesticide product could cause serious injury to your pet".
- Products with concentration of a.i. greater than 6.5% must have child resistant packaging.
- Labels must include the statement: "Children should not be allowed to handle or apply this pesticide product".
- Labels must specify: "For treatment only of mites; treatment of other pests is prohibited."

Dog Shampoos:

- Use will be restricted to certified applicators and veterinarians.
- Protective clothing required for applicators: long-sleeved shirts, long pants, full foot covering, elbow-length waterproof gloves, and waterproof aprons.

## E. Requirements for Enclosed Area Sprays

### Moth Sprays

- Applicators will be required to wear MSHA/OSHA approved cartridge respirators.
- Label updates as described in Chapter VIII, J. (see "Requirements for All Uses")

### Fumigation Devices

- Cancel indoor use.

### Uninhabited Building and Storage Bin Sprays:

- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses")

## F. Requirements for Lindane Dusts

- Labels for ALL lindane dust products must be updated as described (see Requirements for ALL Uses) in Chapter VIII, J.

### Seed Treatment:

- Protective clothing required for applicators during manual seed treatment operations: long-sleeved shirt, long pants, gloves, disposable paper dust mask covering at least one-third of face.
- Required label statement: "This product should be applied in a well-ventilated area."

### Dog Dusts:

- Use will be restricted to certified applicators and veterinarians.
- Required label statement: "This product should be applied in a well-ventilated area."

G. Requirements for Below-Shoulder Sprays:

Cucurbits:

- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses")

Christmas Trees:

- Use will be restricted to certified applicators.
- Protective clothing required as described in VII. E. 1. Commercial ornamentals
- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses")

H. Requirements for Pre-Plant Soil Applications

Pineapples:

- Labels must be updated as described in Chapter VIII, J. (see "Requirements for All Uses").

I. Requirements for Other Household Products (Flea Collars, Shelf Paper, and Household Sprays):

- Labels must be updated as described in Chapter VII, J. (see "Requirements for All Uses")
- Required Label Statement: "Avoid exposure to children. Do not allow children to apply or handle this product."
- Required Label Statement for spray or liquid products: "Do not allow children or pets in treated areas until surfaces are dry".
- Products with concentrations of active ingredient greater than 6.5% must have child resistant packaging.

J. Requirements for All Uses

- Mutagenicity testing aas described on pp. 71-72. NOTE: A voluntary agreement with CIEL has been reached for completion of first priority tests 12 months after publication of the notice of availability of PD-4 or agreement on protocols by CIEL and EPA scientists, whichever is the later. Selection and completion of secondary priority tests to be discussed after completion of first priority tests.

- All Household Use Products must contain the following label statement: "Do not allow children to handle or apply this pesticide product".

- No Aerial uses

- No Aquatic uses

- Labelling updates: ALL REGISTRANTS must update their labels to include:

    - proper handling

    - proper disposal

    - symptoms of poisoning (for applicators, and for pets where appropriate)

    - practical treatment in event of poisoning (for applicators, and for pets where appropriate)

    - other warning statements appropriate for the product's toxicity category

# APPENDIX 1:

## Comments from the Secretary of Agriculture

November 17, 1980

Honorable Douglas M. Costle
Administrator
U. S. Environmental Protection Agency
Washington, D. C. 20460

Dear Mr. Costle:

This is in response to the U. S. Environmental Protection Agency's Notice of Determination concluding the Rebuttable Presumption Against Registration of Pesticide Products Containing Lindane.

We interacted with EPA in developing the biological, economic, and exposure information according to the current Memorandum of Understanding between our two agencies. Thus, we are pleased to be able to review and comment on this notice and the accompanying position document.

The opening sentence on Page III-1 is incorrectly cited. The full title of the June 1978 report is "Preliminary Benefit Analysis of Lindane prepared jointly by USDA and EPA." The basic biological and economic information contained in the June 1978 and the October 1979 report is the same. Both of these reports were compiled by the joint USDA/States/EPA lindane assessment team. Because of the opening statement on page III-1, our state cooperators have voiced concern that their joint efforts may not be utilized by EPA.

There are areas of agreement as well as issues of concern to us and to the cooperating States. Our comments on these specific items are contained in the enclosure which is an integral part of this response.

The additional time you granted for our review of this document was very beneficial and is appreciated. We are hopeful EPA will give favorable consideration to these suggestions.

Sincerely,

Bob Bergland
Secretary
U. S. Department of Agriculture

Enclosure

## ENCLOSURE
## SECRETARY OF AGRICULTURE'S RESPONSE
## LINDANE NOTICE OF DETERMINATION, PD 2/3

1. We believe that every effort should be made to maintain pest control strategies without causing unacceptable risks to users and the public. We concur with EPA's selection of regulatory options regarding the continued registered uses of lindane on livestock, pineapples, pet washes, and commercial ornamentals with certain label modifications, including "Restricted Use."

2. We concur in EPA's proposed regulatory options of cancellation where the risks appear to exceed the benefits. These include:

   — Household use associated with shelf paper, waxes, sprays and smokes (fumigation devices), and the minor use associated with industrial moth sprays;

   — Pet applications including collars, shampoos and dusts;

   — Insect sprays - uninhabited buildings; and

   — Empty storage bins - fog sprays.

All of these uses involve continuous exposure for which there are adequate substitutes.

3. The precautionary statement, "Do not use lindane products on pregnant or young animals," may be desirable for veterinarians treating household pets. However, it may be impractical or impossible, in many cases, to make pregnancy determinations when livestock herds are being treated. We suggest that this statement be modified to be advisory rather than a label prohibition.

4. We share the EPA's concern for applicator exposure but would like clarification of the exposure calculations used since this was not explained in PD 2/3. Also, we recommend consistency in the selection of available protective clothing. The following label modifications on the use of protective clothing might be considered:

   — Long sleeved shirts and pants.

   — Impervious gloves (rubber or neoprene) and boots.

   — Wide brimmed hats or roof type covers over spraying equipment when overhead spraying on agricultural and/or forestry sites.

   — Approved respirators when handling dust formulations and when spraying in confined spaces.

   — Impervious (rubber or neoprene) aprons in those areas where normal treatment practices could anticipate splashing of the treatment solutions and where aprons do not constitute a hazard around equipment.

5. Livestock - As pointed out in the USDA/State/EPA benefit report, lindane is often used in combination with other pesticides, primarily toxaphene, to control pests on livestock. One of the more popular combinations is lindane (2%) and toxaphene (44%). This combination results in immediate control by lindane coupled with the longer residual activity provided by toxaphene. In developing the final regulatory action for lindane, the regulatory actions taken on toxaphene must also be considered.

   We believe that if the lindane registrations for livestock are retained, but the registered uses of toxaphene are cancelled, the livestock industry would be unable to control certain pest problems.

6. Hardwood Logs and Lumber - The decision to phase out this use over a 2 year period in the absence of effective registered alternatives seems inappropriate considering the extent of anticipated hazard. A July 28, 1980 letter from Southern Forest Experiment Station at Gulfport, Mississippi, to the Documents Control Office of the Chemical Information Division of EPA indicated the limited but critical amounts of lindane used in protecting wood from beetle attacks. As the assessment report notes, there are no chemical or nonchemical alternatives available for the registered uses of lindane on hardwood logs and lumber. Chlorpyrifos is not registered for use on felled hardwood logs and lumber and there are no assurances that it will be effective and that such registrations will be obtained. It is questionable as to whether 2 years is sufficient time for registrants to develop and have reviewed by EPA the volume of data needed for a new registration of this type. We therefore suggest that EPA give further consideration to the adoption of Option 2 (continued registration) with the appropriate label modifications to reduce exposure.

7. Seed Treatment - We are concerned about the impact of the proposed cancellation of lindane as a seed treatment. The absence of an effective seed protectant results in insect injury to the seed with the resulting loss of plant stand, plant vigor, yield losses, and increased susceptibility to disease organisms. Some of these losses may necessitate the time and expense of replanting which results in yield losses due to the shortened growing season. EPA indicated that lindane seed treatments are applied as insurance treatments. Because of the pests involved, this is the only procedure that is practical and applies equally to the alternatives. Most crops are planted when soil temperatures are low. Lindane is effective and stable at these lower soil temperatures while the alternatives generally are not.

   There are no seed treatment alternatives for small grains, dry peas and beans, lentils, sorghum, sunflowers, sugar beets, and vegetables. In actual practice, the small grain producer that uses lindane seldom treats his own seed, but purchases it already treated. Lindane is registerd and effective for the control of seed corn beetles, seed corn maggots, and wireworms. The possible alternatives to lindane on corn are diazinon and chlorpyrifos. Diazinon is not registered as a seed treatment for wireworms, and chlorpyrifos is only registered as a seed treatment for control of seed corn maggot. Therefore, without lindane, wireworm problems can be expected to increase to the extent that significant crop losses will occur. The alternatives can only be applied as a planter box treatment to corn.

Lindane, however, can be applied similarly, as a slurry treatment seed dealer or elevator), and in advance of planting by automatic seed treaters that meter the proper amount of material directly to seeds during the planting process.

These latter two options, which are essentially closed systems, should be considered as a means of reducing potential exposure, in lieu of cancellation.

8. Avocados - We support the delayed "final decision" on this use until the University of Florida has had an opportunity to finalize its data on the avocado/mirid project. We believe that since this is truly a minor use, with no effective alternative controls available to producers, every consideration should be given to regulatory options to retain this registration.

9. Ornamentals - As previously stated, we agree with the continued registration of lindane on ornamentals (including greenhouse and nursery plants) by commercial applicators.

   Because continuous exposure is not involved and there are no satisfactory subsitutes, we further recommend that registrations for lindane be retained for homeowner use on ornamentals with appropriate label modifications to reduce possible exposure. This use is only on an "as needed" basis and usually requires no more than one application every year or every few years. As pointed out in the PD 2/3, lindane is the only material registered for the control of all major borer species on woody ornamentals.

10. Curcurbits - Lindane is registered for the control of a wide range of insects on cantaloupes, cucumbers, pumpkins, squash, and watermelons. This is not true for any of the alternative insecticides identified in PD 2/3. The USDA/State/EPA benefits report indicates that significant increased treatment costs can be expected from the cancellation of lindane for these uses. Most of the alternative insecticides may be more hazardous to the applicators, beneficial insects, and pollinators, and require more frequent applications. Therefore, we suggest the selection of Option 2 providing for the continued registered use on curcurbits.

11. Minor Uses - There are minor use registrations not specifically addressed in either the USDA/State/EPA benefits report or in PD 2/3 that are important to regional or local areas and Puerto-Rico. Of importance in the continental United States are preplant treatments labeled for the control of soil insects attacking celery, cucumbers, kale, lettuce, melons, pumpkins, spinanch, and tomatoes. Of particular interest outside the continental U.S. are the control of the West Indian sugarcane root borer weevil and white grubs on sugar cane, symphylans and grubs in pineapples, cutworms and white grubs on vegetables, foliage applications for the control of scales, white flies and other foliage insects of mangos, lace bugs on ornamentals, registrations be retained with appropriate label modifications.

12. Christmas Trees - The principal insects of concern on Christmas trees are the white pine weevil, the pales weevil, and the pine root weevil. The white pine weevil attacks new terminal growth, and this is the

only area that requires treatment. Therefore, insecticidal applications can usually be made with compressed air, handgun, or backpack equipment which deliver coarse droplets. The only registered alternative for this use, oxydemeton-methyl (Metasystox-R), costs up to two times that of lindane. This insecticide is more toxic than lindane, especially from a dermal exposure aspect.

The pales weevil and pine root collar weevil are attracted to recently cut pine stumps where they begin their life cycle in the roots of cut stumps. The most appropriate control for these insects is to make insecticidal applications to the cut stumps and adjacent soil. These treatments are normally applied with commercially available boom type sprayers, all of which deliver coarse sprays. In the case of the pales weevil, control must be obtained to prevent reinfestation for the remaining standing trees. Foliar sprays are seldom used for the control of this weevil if cut stumps are treated.

Silvicultural or nonchemical controls including basal pruning, duff removal, stump or slash removal, or two year land fallow have been advocated but are not economically feasible and also increase the possibility of soil erosion. Losses to pines when only nonchemical controls are utilized have been calculated to range from $644 to $1020 per acre. The lower figure considers only equipment and labor costs, the higher figure also includes yield losses (Scotch pines, Michigan). In Pennsylvania, lindane is an essential part of their Christmas tree integrated pest management program.

Due to the nature of the pests involved and the effectiveness of lindane for their control, we suggest that Option 2 be selected. Regulatory options, such as protective clothing and equipment modifications, should be considered as alternatives to cancellation.

13. Pecans - The presently available chemical alternatives for pecan phylloxera control, identified in PD 2/3, include oil or malathion. These chemicals are not as effective as lindane; and for six of the major pecan producing States, the use of these products as replacements for lindane would increase control costs by $631,000. For Georgia alone, control costs were estimated to increase $286,000. In these same six States, yield losses were estimated at $742,000. We also question the advisability of substituting endosulfan for this use because of its greater relative toxicity. Lindane is applied once per year so exposure is minimal. Further, there are no nonchemical control alternatives. Until other effective environmentally acceptable control measures are assured for those States having this problem pest, the availability of lindane is essential and should be retained.

14. Forestry - Although lindane is not widely used in forestry, there are a number of locations where its use is critical to continued timber production. PD 2/3 is in error when it states that "a variety of chemical alternatives are presently registered" for forestry uses. For the mountain pine beetle, Dendroctonus ponderosae Hopkins, a major forest insect pest in many western areas, only three pesticides are registered: lindane, ethylene dibromide (EDB), and cacodylic acid. Both EDB and cacodylic acid are currently under Rebuttable Presumption Against Registration (RPAR) review and it appears likely that the

forestry uses of EDB will be cancelled. Problems associated with the critical timing and method of application of cacodylic acid makes use of that chemical almost nonexistent. Further, the use of trap trees is not possible in very many situations, primarily because of the need to treat so many trees within a very limited amount of time.

Ips spp. and the spruce beetle, Dendroctonus_rufipennis (Kirby), are two other important bark beetles in the West for which lindane and EDB are the only chemicals reasonably useful for direct control.

We do not believe chlorpyrifos, dicrotophos, and endosulfan can be considered alternatives to lindane. Forest Service research indicates that chlorpyrifos is ineffective against the mountain pine beetle. Dicrotophos and chlorpyrifos do not control the spectrum of insects that are controlled with lindane and are more expensive. Dicrotophos and endosulfan are acutely toxic and present a real hazard to applicators far greater than lindane. In addition, endosulfan is limited to use on logs.

Along the Colorado Front Range and in South Dakota, there are many mountain areas where private landowners treat bark beetle infested trees with lindane. This is not a typical forestry application, but the chemical is used in a forest environment and cannot be considered an ornamental use. Although the Forest Service does not have data on the amount of lindane being applied this way, based on the number of citizen inquiries received, we are sure that a substantial amount of lindane is being used. Lindane is the only chemical available to homeowners for the treatment of bark beetles, because the formulators of the EDB-registered products only sell to State or Federal agencies.

To reduce losses from bark beetles on an area-wide basis, a combination of methods is used. Various tools are necessary for satisfactory production of forest products at economical prices. Where insect infested timber is accessible and economically valuable, salvage logging is used to reduce the insect population and, at the time same time, recover some value. Silvicultural practices are utilized to provide long-term protection from bark beetle epidemics. High value trees in recreation areas and around homes are sprayed to prevent attack. Nonchemical and silvicultural controls are useful, but not applicable to all areas and situations. Direct control using lindane or EDB is used on infested trees where the other methods are not practical due to terrain, timber value, or other factors. If lindane is cancelled, one important tool of this integrated approach is lost.

However, we agree that one of the major impacts of cancellation will be to the small private landowners in the South. Salvage logging of beetle infested and uninfested green buffer trees is the only effective suppression technique that can be used during severe infestations. The cut-and-leave without chemical treatment alternative is the one most widely used when salvage is not practical. This method is only effective during the hot summer months when the beetles are most active. Heat is needed to drive the beetles out of the infested logs before they have fully developed, thus stopping the spread of the infestation. However, the best time to control the beetles is when they are in the trees during the colder winter months. This is when the cut-and-spray (lindane) treatment must be used.

of the questions of concern about this product is the possible adverse effect on human health when used inside the home. The Wood Preservative Assessment Team has recommended that PCP not be used in the home, and some labels already carry this statement. Because the hazards of PCP preclude its use inside dwellings, it cannot be considered an alternative to lindane. Lindane is effective for the control of the wood boring insect complexes, dry wood termites, and there are no other safe effective alternative control measures. We suggest the adoption of Option 2 (continued registration). Label modifications are suggested in lieu of cancellation.

# APPENDIX II:

## Comments from the Science Advisory Panel

# FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

## SCIENTIFIC ADVISORY PANEL

### Review of Preliminary Notice of Determination Concluding the Rebuttable Presumption Against Registration (RPAR) of Pesticide Products Containing Lindane

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The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel has completed review of plans by the Environmental Protection Agency (EPA) for initiation of regulatory action on pesticide products containing Lindane under the provisions of Section 6(b)(1) of FIFRA as amended. The review was completed in open meetings held in Arlington, Virginia, during the period July 24, 1980, and August 13-14, 1980.

Maximum public participation was encouraged for the review. Public noticies of the meetings were published in the Federal Register on July 3, 1980, and July 25, 1980. In addition, telephone calls and special mailings were sent to the general public who had previously expressed an interest in activities of the Panel. Written and oral statements were received from the technical staff of the Environmental Protection Agency, and from representatives of the Centre International d'Etudes de Lindane, the National Pest Control Association, the National Association of Wheat Growers, the Paper Products, Inc., North Dakota Crops Council, Oregon Wheat Growers League, Washington Wheat Commission, Rachel Carson Council, Inc., Idaho Wheat Commission, Athena Products Corporation, University of Idaho, and the North Dakota State Wheat Commission.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency and other parties, the Panel unanimously submits the following report:

Lindane, the gamma-isomer of hexachlorocyclohexane, appears to be the least hazardous of the widely used organochlorine insecticides. Available data suggest that lindane is at worst a weak animal carcinogen, may have a low degree of fetotoxicity, may disrupt reproductive processes, and can produce central nervous system excitability after oral and dermal ingestion. The Panel agrees with EPA that Lindane is substantially more toxic to young than adults in both humans and domestic animals and that chronic exposure can sometimes result in disastrous blood dyscrasias.

However, for certain uses in insect pest control, e.g. scabies, bark beetles and powder post beetles, and seed treatment for wireworms, Lindane has no available substitutes and these and certain very limited applications in agriculture and protection of ornamentals are both essential and well suited to Integrated Pest Management procedures. Furthermore, the total amounts of Lindane used for these uses, e.g. < one million pounds annually, represent a minimal hazard to the environment.

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Therefore, the Panel has the following comments and recommendations:

1. Household uses of Lindane in treated shelf paper and floor waxes provide an unwarranted risk to the householder and should be cancelled immediately.

2. Pet uses for unrestricted use as flea collars, dog dusts, and dog shampoos should be cancelled immediately. Veterinary medical preparations of Lindane for use in mange and scabies and for flea, louse and tick control should be available as collars, powders, sprays, shampoos, and dips under restricted classifications for use by licensed veterinarians only with label cautions and requirement for protective clothes, as proposed by EPA.

3. Ornamental applications for unrestricted use by the homeowner should be cancelled immediately. Ornamental uses restricted to commercial operators should be continued with full warning label cautions about the hazards of cancer, fetotoxicity, and central nervous system effects and a caution that women of child-bearing age and children must avoid exposure. Full protective clothing must be worn.

4. Lindane registrations for powder post beetle control should be continued under restricted classification for use by registered Pest Control Operators with full warning label cautions and full protective clothing proposed by EPA.

5. Livestock applications should be placed under restricted classification for use by certified applicators only with full warning label cautions and mandatory protective clothing as proposed by EPA.

6. Uses on pineapples should be retained with warning label cautions proposed by EPA.

7. Uses on cucurbits should be continued under restricted classification with full warning label and mandatory protective clothing proposed by EPA.

8. Uses on avocadoes should be continued under restrictive classification with full warning label and mandatory protective clothing proposed by EPA.

9. Uses on pecans should be continued under restricted classification with full warning label and mandatory protective clothing proposed by EPA.

10. Uses on Christmas trees should be continued under restricted classification with full warning label and mandatory protective clothing proposed by EPA.

11. Uses in forestry for bark beetle control should be continued under restricted classification for application by certified operators with full warning labels and mandatory protective clothing as proposed by EPA.

12. Applications to hardwood logs and lumber should be continued under restricted classification with full warning labels and mandatory

protective clothing as proposed by EPA. Special caution should be given to improving work place practices and disposal of treated sawdust and shavings.

13. Seed treatment uses of lindane should be continued under restricted classification by certified applicators with full warning labels and mandatory protective clothing proposed by EPA. Testimony presented to the Panel suggests that 90% of Lindane seed treatments are made with closed mechanical systems that essentially eliminate operator exposure. EPA should sponsor an educational program to make use of such closed mechanical seed treatment systems universal.

14. The suspicion that Lindane interferes with reproductive processes (hormones) indicates that a 3-generation reproductive study should be performed on an appropriate laboratory animal.

FOR THE CHAIRMAN:

Certified as an accurate Report of Findings:

H. Wade Fowler, Jr., Ph.D.
Executive Secretary
FIFRA Scientific Advisory Panel

DATE: October 6, 1980

# APPENDIX III:

# EXPOSURE ANALYSIS

## INTRODUCTION

This appendix describes, for each use of lindane:

- the exposure assumptions and estimates made in PD 2/3,
- comments received by EPA about those assumptions, and
- EPA's final assumptions regarding exposure associated with that use.

Please refer to Table 3 for a comparison of PD 2/3 and PD 4 exposure estimates.

Readers who are interested in seeing the mathematical steps used to derive exposure estimates from these assumptions may request a copy of the "Lindane PD 4 Exposure Tables". These are available from the Lindane Project Manager, Office of Pesticide Programs, U.S. EPA, 401 M St, S.W., Washington, D.C., 20460.

## I. ABOVE-SHOULDER SPRAYS - AIR BLAST AND POWER HAND GUN

### A. Ornamentals - Commercial Applicators

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that dermal and respiratory exposure to applicators during lindane treatment of ornamentals could be estimated using the model of Wolfe et al. (1974) as determined during hand-pressure spraying of fenthion for mosquito control. A 0.5% w/w lindane solution was assumed. It was also assumed that a commercial applicator worked 3-8 hours a day for 1-15 days per year. The cohort at risk for commerical applications was estimated to be from 30-1200.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) agreed with the Agency's choice of Wolfe et al. (1974) as a model for estimating exposure during application of lindane to ornamentals. In this study, exposure estimates were made during mosquito control operations using hand pressure sprayers. However, Edwards used an approximate mean cohort-at-risk figure of 600 people in place of the 30-1200 range used in PD 2/3. Edwards also suggested that 0.06% is a more reasonable use dilution, based on USDA recommendations.

Both Nielsen (1982) from the Ohio Agricultural and Research Center, and Felix (1982) from the National Arborist Association, agreed that a commercial applicator would be exposed to much larger volumes of lindane spray than a homeowner would. Protective clothing is currently worn, however. They also believed a more reasonable estimate of exposure duration for commercial applicators would be eight hours a year.

#### 3. The Agency's PD 4 Response

The following protective clothing measures are assumed in the PD 4 exposure analysis: a long-sleeved shirt, long pants, shielded hard hat, and impermeable gloves. It is assumed that this protective clothing reduces dermal exposure by at least 80%. In some cases, rubber raincoats and respirators are also worn.

Based on reevaluation of label data, the Agency agrees that a 0.06% final use concentration is a more reasonable estimate than 0.5%. The Agency also agrees that a mean value of 600 persons at risk is a reasonable estimate to use.

For estimating exposure to commercial applicators, the Agency uses a model which measured exposures during power hand gun spraying of fruit orchards from a portable machine using dieldrin. Exposure duration is assumed to be eight hours per year for commercial applicators.

## B. Avocados

### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that spraying operations for avocados were identical to those for other fruit orchards, and that applicator exposure could be estimated using the models in Wolfe et al., 1967. Based on the Wolfe study, dermal and respiratory exposures were 50 and 0.1 mg/hr respectively. A single pest control operator was assumed to treat one average avocado farm in one 8-hour day, twice a year.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), did not disagree with the use of the exposure data contained in Wolfe et al. (1974). However, he recommended using more appropriate exposure values for 0.05% sprays, i.e. 22.5 mg/hr for dermal and 0.035 mg/hr for respiratory exposures.

### 3. The Agency's PD 4 Response

The Agency has evidence (Day, 1982) that protective clothing is not currently being worn by most applicators during spray operations with air blast equipment. If protective clothing measures (such as a long-sleeved shirt, long pants, impermeable gloves, wide-brimmed hat or a roof-type shelter on the machinery employed) were worn, it is estimated that dermal exposure would be reduced by about 80%.

The Agency reevaluatated the data in the Wolfe et al. (1967) paper, and calculated new expected values of 20 mg/hr and 0.04 mg/hr for dermal and respiratory exposures, respectively. However, studies show dermal exposure varies considerably during air blast spraying, generally within the range of 2-50 mg/hr with 40 mg/hr being the most frequent (Day, 1982). Therefore, the Agency has used 20 mg/hr and 0.04 mg/hr for dermal and respiratory exposure, respectively, to estimate exposure during air blast spraying of avocados.

## C. Pecans

### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that exposure to applicators applying lindane (0.05% w/w) to pecan orchards was comparable to applicator exposure during spraying of other fruit orchard crops, i.e., 50 mg/hr and 0.1 mg/hr for dermal and respiratory exposures, respectively (Wolfe et al., 1974). No protective clothing was assumed. A single pest control operator was assumed to treat one average pecan farm in one day, once a year.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) suggested that more reasonable values from the Wolfe et al. (1974) paper should be used by the Agency. He suggested that for a 0.05% spray, 22.5 mg/hr was more appropriate than 50 mg/hr for estimating dermal exposure, and that 0.035 mg/hr was more reasonable than 0.1 mg/hr for estimating respiratory exposure.

### 3. The Agency's PD 4 Response

The Agency has evidence (Day, 1982) that protective clothing is not currently being worn by most applicators during spray operations with air blast equipment. If protective clothing measures (such as a long-sleeved shirt, long pants, impermeable gloves, wide-brimmed hat, or a roof-type shelter on the machinery employed) were worn, dermal exposure would be reduced by an estimated 80%.

Dermal exposure during air blast spraying generally varies from 2-50 mg/hr (Day, 1982) with 20 mg/hr being the most frequent. Therefore, the Agency has used the estimate of 20 mg/hr, to estimate exposure during air blast spraying of pecans.

## D. Livestock

### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that an applicator's exposure in dipping operations was negligible in comparison to spray operations. It was also assumed that an applicator's exposure to lindane (0.045% w/w) during spray operations was comparable to exposure during mosquito control operations (Wolfe et al., 1974) using a fenthion (0.06% w/w) spray. No protective clothing was assumed. The cohorts at risk were estimated to be 248,000 persons, and an applicator was estimated to be exposed 2.1 - 2.4 hours a year.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) agreed with the Agency's assumption that dipping of livestock is rare compared to spraying. He also agreed with the Agency's choice of surrogate models. Edwards presented evidence that applicators usually wear protective clothing and respirators.

### 3. The Agency's PD 4 Response

Sufficient evidence was submitted to the Agency that protective clothing is currently being worn by commercial applicators spraying lindane on livestock. The following protective clothing measures are assumed in the PD 4 exposure analysis: a long-sleeved shirt, long pants, aprons, boots, respirators, and impermeable gloves. It is assumed that this protective clothing reduces dermal exposure by at least 80% and respiratory exposure by at least 90%.

The Agency reevaluated use patterns for spraying livestock with lindane, and in the PD 4 exposure analysis, uses another model which more accurately reflects the exposure potential than that model used in the PD 2/3 analysis. The Agency uses exposures from the spraying of dieldrin to fruit orchards with a power hand-gun from a portable machine using a dieldrin spray.

## II. ABOVE-SHOULDER SPRAYS: BACKPACK OR HAND PRESSURE EQUIPMENT

### A. Ornamentals - homeowner applicators

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that dermal and respiratory exposure during lindane treatment of ornamentals could be estimated using the model of Wolfe et al. (1974) as determined during hand-pressure spraying of fenthion for mosquito control. A 0.5% w/w lindane solution was assumed. It was also assumed that a homeowner would spray only one hour/year. The cohort at risk for homeowners was estimated at 75,000.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) agreed with the Agency's choice of Wolfe et al. (1974) as a model, but suggested that 0.06% is a more reasonable use dilution, based on USDA recommendations.

Both Nielsen (1982) from the Ohio Agricultural and Research Center, and Felix (1982) from the National Arborist Association, agreed that for estimating homeowner exposure while spraying ornamentals, the mosquito control model was reasonable for the Agency to use. However, they both agreed that homeowner applicators would be exposed to much lower volumes of lindane spray than commercial applicators. For homeowners, the PD 2/3 value of one hour per year was considered reasonable.

#### 3. The Agency's PD 4 Response

The Agency assumes that protective clothing is not currently worn by homeowners applying lindane to ornamentals, and that there is exposure duration of one hour per year. Based on reevaluation of label data, the Agency agrees that a 0.06% final use concentration is a more reasonable estimate than 0.5%. As recommended by Nielsen and Felix, the mosquito control model is retained for estimating homeowner exposure.

### B. Forestry

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that applicator exposure to lindane (0.5% w/w) using backpack sprayers during forestry operations was comparable to applicator exposure using hand-pressure sprayed fenthion (0.06% w/w) solutions for mosquito control. Applicators were estimated to treat 32 trees/day, 5 minutes/tree, 30 days/year.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) agreed with the Agency's use of a back-pack sprayer as representative equipment in forestry operations, with a 0.5% lindane concentration, and with the Agency's choice of a surrogate model, i.e. Wolfe et al., 1974.

Edwards pointed out that an error occurred in the PD 2/3, where it was stated that one applicator treats 32 trees/day. According to Edwards, the Agency's backup document for the PD 2/3 Exposure Analysis (EPA, 1980b) had two applicators treating 32 trees/day.

Laut (1982) from the Colorado State Forest Service, and Johnson (1982) from the USDA Forest Service in Colorado, said that protective clothing measures actually worn include gloves, long pants, long-sleeved shirt, boots (often) and a hard hat (often). Both agreed that the other assumptions were reasonable.

### 3. The Agency's PD 4 Response

The following protective clothing measures are assumed in the PD 4 exposure analysis: a long-sleeved shirt, long pants, and impermeable gloves. It is assumed that this protective clothing reduces dermal exposure by at least 80%.

A study more appropriate than the Wolfe et al. (1974) study for estimating exposure to forestry personnel has been published in the literature and used in the PD 4. Lavy et al. (1980) estimated exposure levels to forestry personnel who apply 1.9% w/w 2,4,5-T by back-pack sprayers to be 26.7 mg/hr and 0.027 mg/hr for dermal and respiratory exposures, respectively.

The Agency agrees that an error was made in translating the information from the PD 2/3 revised exposure analysis to the actual PD 2/3. The text of the PD 2/3 should have read that two applicators treated 32 trees per day (40 hours per year per applicator).

## III. CRAWL SPACE TREATMENTS

### Structures

### 1. The Agency's Exposure Calculation with PD 2/3

For evaluating lindane exposure to applicators during crawl space treatment for powder post beetles, the Agency used a model based on Batchelor and Walker (1954), where a 0.05% parathion solution was hand sprayed in fruit orchards. A spraying time of one hour per day, 10-20 days per year was assumed. The cohort at risk was estimated to be 500-1000 persons. A 0.5% w/w lindane solution was assumed. It was assumed that no protective clothing was worn.

For evaluating lindane exposure to residents after powder post beetle treatment, the Agency used data from the United States Public Health Service (USPHS) Communicable Disease Center (PHS/CDC, 1952). In this study, lindane was deposited on surfaces at a rate of 25 mg/ft$^2$, and then room air samples were taken at intervals for 8 days. An 85-day weighted average of 0.05 ug/l (or 0.05 mg/m$^3$) was used. Occupants were assumed exposed for 24 hours a day, 84 days a year, and it was assumed that 10,000 homes were treated annually.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) disagreed with the Agency's choice of models for evaluating exposure to home occupants after lindane treatment for powder post beetles. According to Edwards, EPA had little justification for the assumption that surfaces with lindane deposits of 25 mg/ft$^2$ were saturated with lindane. Much of the lindane would be adsorbed tightly on the wood, particularly if the wood were dry, so that the lindane would not be available for vaporization. Also, the study refers to lindane concentrations in a closed room, where air concentrations would be higher than in a ventilated room. According to Edwards, Queen (1953) showed that most of the lindane contaminating the surface of a building at a rate of 5.2 ug/in$^2$ (0.75 mg/ft.$^2$) disappeared within 6 days.

Concerning ventilation rates, Edwards criticized the Agency for not including an air exchange rate of 3 per hour, which had been used for other uses in the PD 2/3. As for the EPA assumption that the whole basement area would be treated, Edwards pointed out that lindane is usually limited to spot treatments. Of all the assumptions made by EPA, Edwards most strongly disagreed with the assumption that an infested home would be treated every year. Edwards felt a more reasonable estimate for an infested home would be treatment every 10 years.

As for evaluating exposure to applicators, Edwards agreed with the Agency's use of Batchelor and Walker (1954), although he believed the exercise was academic,, because treatments are usually done by professional applicators who would be wearing protective clothing.

Concerning the Agency's estimate of cohort at risk (500-1000 persons), the National Pest Control Association (comment #5B) estimated that over 4,000 applicators are involved in application of lindane for control of wood-destroying pests.

A more appropriate model for estimating exposure was brought to the Agency's attention (via personal communication, not as an official rebuttal comment) by Carr, from the National Pest Control Association. He pointed out a study by Maddy et al. (California Department of Food and Agriculture, 1979) which estimated applicator and home occupant exposures to chlordane during crawl space treatment.

### 3. The Agency's PD 4 Response

Sufficient evidence was submitted to the Agency (Edwards, from CIEL; Carr, from the NPCA; Williams, from the USDA Forest Service, Southern Forest Experiment Station) that protective clothing is currently being worn by applicators spraying structures with lindane. These protective clothing measures include a long-sleeved shirt, long pants, impermeable gloves, and a cartridge respirator.

Based on extensive telephone conversations with Williams (USDA Forest Service, Southern Forest Experiment Station, Gulfport, MI) and Carr (NPCA), the Agency has fine-tuned the time estimates for applicator exposure, assuming now that an average crawl space takes three hours to treat, and that an average applicator does 5 lindane crawl space treatments per year.

For estimating exposure to residents after lindane crawl space treatment, the Maddy et al. (1979) study is used. Living area air was monitored for chlordane residues at intervals up to 30 days (at which time no chlordane residues were detected) after application. It is assumed that lindane air levels will be no greater than these chlordane levels for crawl space treatment where 0.5% w/w lindane is used, compared with 1% w/w chlordane. It is assumed that respiratory exposure could occur to residents for up to 30 days, once every 10 years.

## IV. DIPS

### A. Hardwood logs and lumber

### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions to estimate applicator dermal exposure: no protective clothing was worn; the exposed skin area included head, neck, "V" of chest, hands, and forearms; operators were exposed to a cumulative dose equivalent to a single wetting of all exposed skin; a 0.5% w/w solution of lindane was used; 7 ml of aqueous solution wets an average pair of hands (0.082 $m^2$) up to the wrist; an applicator would be exposed 8 hours a day, 5 days a week, 50 weeks a year.

To estimate respiratory exposure, the Agency assumed the following: all surface areas around the dip vat were saturated with lindane; a saturation vapor concentration of lindane at 20°C of 0.5 ug/1; 10% of lindane saturation represents the best estimate of air concentration; an adult male breathing rate of 1.8 $m^3$/hr.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing the Centre International d'Etudes du Lindane (CIEL, comment #94), submitted information showing that about 35% of lumber is treated by the green chain dip vat method, and 65% by the lumber package dip vat method. In the latter procedure, the packages are handled by fork lift trucks and are not touched by the workers. A 0.056% treatment solution is used, made from 1 pint of 11% w/w lindane in 20 gallons of water. Edwards estimates that work gloves are universally worn, and that hard hats are worn in more than 90% of the mills.

As a model for estimating respiratory exposure near a dip vat, Edwards suggested using a study (PHS, 1952) in which the walls of a closed room were saturated with lindane, giving an average lindane concentration in the air of 0.208 ug/1.

Concerning the number of hours worked handling treated lumber, Edwards estimated, based on several inquiries to the hardwood industry, that a 4-hour exposure per day, a 5-day working week, and a 40-week exposure per year would be more reasonable estimates to use.

USDA commented (see Appendix 1) that appropriate label modifications to reduce exposure should be considered. The protective clothing USDA recommended were long-sleeved shirts, pants, impervious gloves, and boots. USDA also recommended that impervious aprons should be required in areas where normal treatment practices could probably lead to splashing of the treatment solution and where aprons do not constitute a hazard around equipment.

Zoecon Corporation (1981) submitted a study to the Agency in which lindane air concentrations were measured at various locations in a southern hardwood mill during borer treatment with lindane. Evidence was also submitted by Zoecon that protective clothing is routinely worn in hardwood mills.

### 3. The Agency's PD 4 Response

Sufficient evidence was submitted to the Agency by CIEL representatives that protective clothing is currently being worn in the hardwood industry. These protective clothing measures include a long-sleeved shirt, long pants, rubber apron, impermeable gloves, and a hard hat. Although dermal exposure is possible, it is assumed to be negligible when this protective clothing is worn.

Based on a study conducted for Zoecon (1981) in a southern hardwood mill during borer treatment with lindane, the average lindane air concentration is assumed to be 0.0059 mg/m$^3$.

The Agency accepts the Zoecon estimate that an 8-hour daily exposure, a 5-day working week, and a 40-week exposure per year are reasonable conservative work estimates to use.

## B. Dog Dips

### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual data were available, the Agency made the following assumptions to estimate exposure to veterinarians using lindane dog dips: a veterinarian exposed both hands to a dilute product 5 minutes a day, 26 times a year; the final concentration of lindane was 0.085 g/ml; 7 ml of solution "just wet" hands; no respiratory exposure occurred; and no protective clothing was assumed. For estimating the exposure to dog owners after their pets have been treated with lindane, the Agency assumed the following: lindane volatilized from the hair of the animal, and this volatilized lindane was 100% respirable; the Agency did not feel it was possible to quantify dermal exposure which occurs after dipping; the animal has access to 12,000 ft$^3$; use of lindane was 0.236 mg/ml of final solution for post-dip exposure; after towel drying, 79 ml of wash solution was retained by a small dog, 237 ml by a large dog; exposure after a dog was dipped lasted for 72 hrs, once a year; a dilution factor of 10 was assumed for air exchange; and the breathing rate was 1.2 m$^3$/hr.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) argued that EPA's assumption of 7 ml wetting the hands was unrealistic. 2.5 ml was more likely, based on simple laboratory experiments performed by Edwards.

For estimating respiratory exposure, Edwards recommended using the data from Queen (1953), which showed that 1 gram vaporizing into a 1300 ft$^3$ room for 24 hours gave a concentration of 0.4 ug/l of lindane in air. A 50% lung absorption factor was used, as was the estimate that a dog spends 16 hours/day in the house.

### 3. The Agency's PD 4 Response

Insufficient evidence was submitted to the Agency that protective clothing is currently being worn by veterinarians dipping dogs with lindane. If the following protective clothing measures were worn (a long-sleeved shirt, long pants, and impermeable gloves), it is estimated that dermal exposure would be reduced by 80%.

The Agency agrees with Edwards that the PD 2/3 model was too hypothetical, and contained a significant math error (5 min/60 min which should have been 60 min/5 min). However, the Agency does not have an obvious surrogate study to use as an appropriate model. Therefore, the Agency assumes that dermal exposure while dipping dogs is no greater than the dermal exposure of 3.6 mg/hr during mosquito control operations, using 0.06% fenthion sprays (Wolfe et al, 1974). As in the PD 2/3, veterinarians are assumed to be exposed 5 minutes/day, 26 days/year.

For estimating post-treatment exposure to dog owners or home occupants after lindane treatment, a different model is used in the PD 4 because, as with the veterinarian exposure, the PD 2/3 model was too hypothetical. Therefore, the Agency assumes that lindane indoor air concentrations are no greater than 0.002 $mg/m^3$, which is based on average lindane air concentrations in a closed room where a lindane mothproofing product was being used inside a wardrobe (Haag and Prugmayer, 1981). Because this value represents an actual lindane air concentration in a room without normal ventilation, an additional air exchange rate of 3 exchanges per hour is figured into the Agency's calculations.

The following additional assumptions are made in the PD 4: there will be potential respiratory exposure for three days after the dog is dipped, once a year; there is 100% lung absorption because lindane is in the vapor state; residents spend an average of 15 hours per day indoors; these residents have an average breathing rate of 0.64 $m^3/hr$. (For an explanation of the last two assumptions, please refer to SHELF PAPER, EPA's PD 4 Response).

### C. Dog Shampoos

#### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions to estimate applicator exposure: the concentrate came in direct contact with the shampooer's hands; per washing, a total volume of 15 ml of soap came in contact with the hands; contact time with the concentrate was 3 seconds, with the diluted soap was 5 minutes per dogwash; 7 mls "just wet" hands; there was negligible respiratory exposure during shampooing; and lindane transferred to the oily layer of a dog's pelt.

For estimating post-treatment exposure to pet owners and residents, the Agency assumed that 15 ml of a 0.5% lindane formulation was retained by a small dog, 45 ml by a large dog; the treated animal had access to a 12,000 $ft^3$ area; the resident had a 1.2 $m^3/hr$ breathing rate; lindane volatilized for 72 hours after treatment; there were 26 treatments per year; 100% of the lindane was respired.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), criticized the Agency's assumption of 3 seconds contact with the concentrated solution before soap reaches the hands as "an extremely complex and inapplicable calculation". In his calculations, Edwards used one ml, presumably as the amount that will cover a pair of hands. Edwards did not recommend changing the other assumptions in estimating dermal exposure.

For estimating post-treatment lindane respiratory exposure to pet owners and residents, Edwards suggested slight modifications of EPA's model: that there would be 10 air changes per hour, that a resident would spend 16, not 24 hours a day indoors, and that 50% of the vapors would be respirable.

#### 3. The Agency's PD 4 Response

The Agency assumes that short-sleeved shirts and long pants (but not gloves) are worn by pet owners while shampooing their dogs. The exposed areas get completely wet with the lindane shampoo solution. Based on a laboratory study evaluating water retention on hands (Weaver, 1977), the Agency assumed that 0.01 ml of water/shampoo solution covers one $cm^2$ of exposed skin area, during one shampoo application. Pet owners are assumed to wash their dogs once per year.

For estimating post-treatment respiratory exposure to residents and applicators, the same assumptions were used for the dog shampoo use as for the dog dip use (Please refer to Dog Dip - The Agency's PD 4 Response).

## V. ENCLOSED AREA SPRAYS

### A. Industrial use moth sprays

#### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions to estimate exposure during application of industrial lindane moth sprays: no dermal exposure; an aerosol of 0.1% lindane produced 50% particles of 10 microns or less, and 50% between 10 and 40 microns; 90% of the spray impinged on clothing; clothes were treated in a well-ventilated area for 2 minutes; lindane concentrations in the vicinity of the spray and at the time of spraying were similar to those of 30% freon 12 formulation, which was 44.25 ppm in the breathing zone; spraying was repeated 26 times per year.

To estimate respiratory exposure to occupants after lindane treatment, the Agency assumed the following: 28 grams of 0.1% spray were used every 2 weeks, year-round; vaporization was continuous over a 2 week period, at which time all the lindane would be vaporized; volume of the work space was 6000 $ft^3$; the air exchange rate was 3 per hour; exposure was 10 hours/day, 365 days/year; vapors were 100% respirable.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), disagreed that an aerosol has a particle range from 1-40 microns. He also said an air turnover rate of 1 per hour seemed low. However, Edwards did not disagree with the Agency's choice of models.

For estimating occupant exposure to industrial moth sprays, Edwards agreed with the Agency's model, except he thought it would be better to assume that volatilization is complete after one week (not two) and that 50% (not 100%) of the particles would be of respirable size.

### 3. The Agency's PD 4 Response

A recent study was submitted to the Agency by the Penick Corporation, which measured dermal (0.41 mg/min) and respiratory (2.3 $mg/m^3$) exposures to home applicators using resmethrin formulated in a pressurized container. In the Agency's opinion, this is a reasonable model for estimating applicator exposure to lindane during the spraying of commercial establishments.

Consistent with the assumptions made for the household and pet uses of lindane, it is assumed that there is potential for building occupant exposure for a three day period, at which time all the lindane will be vaporized. All of the vaporized lindane is assumed respirable.

Other assumptions include the following: building occupants spend an average of 8 hours/day, 225 days/year in the exposed area (but since the lindane is completely vaporized after three days, the actual assumed exposure is 78 days/year); there are 3 air changes per hour; an average breathing rate for light work is 1.2 $m^3$/hr.

## B. Fumigation devices

### 1. The Agency's Exposure Calculations in PD 2/3

Based on a study of lindane air concentrations following fumigation (WARF Institute, Inc., 1970), the Agency estimated average concentrations of 0.014 ug/l on a year-round basis, assuming 26 applications a year. It was also assumed that a person spent 24 hours/day indoors, 365 days/year, and that the vaporized lindane was 100% respirable.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), disagreed that treatments would be done every two weeks in homes with no ventilation. Based on the data in Queen (1953), Edwards estimated that lindane treatments would not exceed twice a year, that lindane residues would disappear within 7 days, that there would be an air exchange rate of 3 per hour, that a resident would spend no more than 16 hours a day indoors, and that 50% of the vaporized lindane would be absorbed by the lungs.

### 3. The Agency's PD 4 Response

The Agency has reconsidered the exposure that results from the indoor use of smoke fumigation devices. The Agency's calculations are based on the actual ambient air residue data reported for 21 days by the WARF Institute, Inc. (1970). The Agency assumes all exposure to be respiratory, that a person spends an average of 15 hours per day indoors, and an average breathing rate of 0.64 $m^3$/hr. The Agency did not factor any air exchange rate within the house since the air residues are actual measurements.

The Agency assumed that the smoke fumigation device would be used twice per year.

### C. Uninhabited building sprays / empty storage bin sprays

#### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions to estimate applicator exposure: a 2.2% w/w lindane aerosol solution was used for two minutes, 12 times a year; lindane air concentrations were comparable to spraying of 30% freon solution (44.25 ppm) for 2 minutes (Gay et al., 1975); the breathing rate for light work was 1.2 $m^3$/hr; 1 ppm of lindane in air = 0.0119 mg/l; there was no dermal exposure.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), suggested that the Agency use the data given by Culver et al. (1956) for 5% aerosol application of malathion and chlorthion during mosquito control operations, i.e. an estimated respiratory exposure of 0.28 mg/hr. He assumed 50% of the particles are respirable, and a use dilution of 0.05% lindane.

#### 3. The Agency's PD 4 Response

Because the use patterns are so similar, exposures to applicators while spraying aerosol formulations in uninhabited buildings and empty storage bins are considered together.

The Agency agrees with Edwards that it would be more reasonable to use an actual aerosol study rather than the freon model. Therefore, the Agency uses the suggested Culver et al. (1956) model, which measures dermal values of 6.6 mg/hr and respiratory values of 0.3 mg/hr for 5% sprays. All (100%) of the particles are assumed of respirable size because of the aerosol formulation.

Insufficient evidence was submitted to the Agency that protective clothing is currently being worn by applicators spraying lindane for these uses. If protective clothing measures were worn (a long-sleeved shirt, long pants, and impermeable gloves), it is estimated that dermal exposure would be reduced by 80%.

## VI. DUSTS

### A. Seed treatment

#### 1. The Agency's Exposure Calculations in PD 2/3

For estimating dermal exposure, the Agency assumed the following: all lindane-treated seed was by the manual planter box method, using a 25% w/w lindane dust formulation; the applicator wore no protective clothing; one gram of dust formulation can completely cover hands; 20% of the dust formulation reaches the exposed skin. For estimating respiratory exposure, the Agency used a model based on exposure to cotton dust (US/HEW, 1974). The Agency assumed that average lindane air concentrations around the planter box = 10 mg/$m^3$, that an operator spends approximately 60 minutes per day mixing seed, and that there was 100% respiration of the lindane dust.

## 2. Comments on the Agency's PD 2/3 Calculations

Zoecon Corporation (comment #94) presented the Agency with the details of a field experiment conducted in 1980 which attempted to determine the concentration of lindane in the air during the various operations involved with the "mechanized planter box" method of treating wheat and barley seed. In order to estimate "worst-case" exposure, air samples were purposefully taken downwind in the dust plume. During the treatment operations, filling of equipment, and transfer of treated grain, lindane air levels of 0.7 - 3.6 mg/$m^3$ were present in the plume. During the actual seeding, using either open or closed cab tractors, the potential for lindane exposure was estimated to be from 0.001 - 0.02 mg/$m^3$.

Concerning the Agency's choice of the manual planter box method, versus the mechanized planter box method or seed treated commercially in bulk, Zoecon did not disagree with this choice, stating that with each of the two treatment methods there was dust generated during the movement of seed (commercial) or during the augering process (mechanized). Zoecon agreed that commercially treated seed and auger treated seed produce some (albeit less) lindane dust exposure.

Zoecon submitted a detailed table of typical seed treatment parameters, for both large and small seed types. This table included such parameters as time to seed an acre, seeding speed (acres/hour), time to refill hoppers, total time treating seed, and acres treated in 10 hours. Using the data from this table, Zoecon estimated that seed treatment would take 12 minutes per 10-hour day, two days a year, and that actual seeding would require 10 hours/day, two days/year.

Concerning the particle size distribution of lindane dust which can be respired by an applicator, Zoecon presented evidence (calculated by coulter counter methodology) that 50% by weight of the material is nonrespirable because particles are greater than 30 u in size. Therefore, according to Zoecon, a measured air concentration of lindane in a typical dust should be corrected by at least a factor of 50% by weight for nonrespirable particles. The remaining 50% constitutes exposure, but only 10% of that is by the more significant inhalation route, the other 90% being best compared to an oral administration.

Concerning protective clothing measures, Zoecon stated that cool weather conditions prevalent during the planting season increase the likelihood that protective clothing (long-sleeved workshirt, long pants, impermeable gloves) would be worn to reduce dermal exposure. Zoecon assumed that 1% of the lindane dust would be passed through dust masks, if they were worn.

Concerning the Agency's assumption that 1 gram of fine powder (Bon Ami) covered a pair of hands (0.082 $m^2$), Zoecon repeated the experiment using an inert agricultural formulation (Kaolin), and found that 200 mg (0.2 gram) completely whitened all surfaces of the hands of an adult male. In the absence of contradicting data, Zoecon also assumed, as did the Agency in PD 2/3, that only 20% of the exposed skin area is actually covered with lindane dust.

Edwards, representing CIEL (comment #94), also presented a rebuttal to the Agency's seed treatment exposure estimates. First, Edwards disagreed with the Agency's assumption that only lindane dusts are used for seed treatment, stating that there are a variety of liquid and other formulations (some using "stickers" to improve adhesion) registered for this use. He also disagreed with the Agency's choice of the manual planter box treatment method, arguing that commercially treated seed and auger treated seed are more commonly used. According to Edwards, using the mechanized (auger) planter box method there is "virtually no exposure due to seed treatment" if the applicator wears protective clothing and a face mask during treatment.

Edwards conducted simple experiments similar to those carried out by Zoecon which also indicated that 200 mg (0.2 gram) would be a more reasonable estimate of the amount of formulation to cover a pair of hands than the Agency's PD 2/3 assumption of 1 gram.

Edwards disagreed with the Agency's use of a cotton dust model. In an area of 1000 $m^3$, there would be 10 grams of dust (using the Agency's 10 $mg/m^3$ assumption), meaning that 40% of the dust needed to treat a bushel of seed would be in the air, not on the seed. Edwards does not believe farmers would be likely to waste so much lindane. He considered 1 $mg/m^3$ a more realistic air concentration to use. Concerning particle size, Edwards assumed, as did Zoecon, that 50% of the lindane dust particles were greater than 30 ug and therefore too large for inhalation. Also, Edwards used a formulation which contained 18.75% lindane (also recommended by USDA) rather than the 25% concentration assumed in PD 2/3.

Estimating the various methods of seed treatment, Edwards assumed 10% is treated commercially, 10% is treated by the manual planter box method, and 80% is treated by the mechanized (auger) planter box method. Rather than the one hour/day assumption made by the Agency for time required to treat seed, Edwards assumed that an applicator would have to pour lindane for 2-3 minutes into the planter box, refilling the box four times a day, i.e., 10 minutes of exposure to lindane per day.

### 3. The Agency's PD 4 Response

The rebuttal comments received by the Agency with regard to this use pattern were of excellent quality.

Based on information in the Zoecon rebuttal submission, the Agency will continue to use the manual planter box method as a conservative model for estimating applicator exposure during seed treatment. This is because, according to Zoecon, commercially treated seed and mechanically treated seed produce less exposure than seed treated manually. This assumption is supported by the exposure study by Zoecon, during which air concentrations were measured during "mechanized planter box" treatment.

Based on sufficient evidence submitted to the Agency, it is assumed that protective clothing is currently being worn during seed treatment and this protective clothing includes a long-sleeved shirt, long pants, gloves, and disposable paper masks (worn during seed treatment and hopper fill operations only).

based on information submitted by Zoecon and Edwards, the Agency has revised the exposure time estimates made in PD 2/3, and assumes that seed treatment and hopper fill take 10 minutes per day, 2 days per year.

For estimating dermal exposure, the Agency concurs with the use of 200 mg of dust formulation to cover a pair of hands, rather than the PD 2/3 estimate of 1 gram. The Agency continues to use the PD 2/3 assumption that of the exposed skin area, 20% would be covered with lindane dust.

Concerning the PD 2/3 choice of 25% active ingredient as the most representative formulation for seed treatment, the Agency agrees, based on the rebuttal submissions and Agency verification, that the use of an 18.75% a.i. dust formulation would be more representative of formulations currently being used.

Based on the data in the lindane exposure study submitted by Zoecon, the Agency estimates that lindane air concentrations surrounding a planter box would be 2 mg/m$^3$ and 0.01 mg/m$^3$ during seeding. The Agency accepts Zoecon's assumption that 1% of the dust is passed by the dust mask, but of the 1%, 100% is of respirable size.

### B. Dog dusts

#### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions to estimate exposure to applicators who apply lindane dust to their pets: lindane (1% dust) formulation covered 20% of the exposed skin area; 1 gram of dust completely covered one pair of hands; maximum dust inhaled over 2 minute period = 10 mg/m$^3$; all dust was respirable; no protective clothing was worn; a treatment took 2 minutes and was repeated 26 times a year; and lindane volatilized at a steady rate for 3 days, at which time all lindane would have vaporized.

For estimating respiratory exposure to home occupants after lindane dust treatments, the same assumptions for the dog dip use were made, except that a typical pet treatment required 2 oz of 1% powder per treatment, and a resident would be exposed 12 hours a day, for 3 days, 26 times a year.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94) said that the EPA assumptions should be modified the same way for dog dust as for seed treatment (also a dust), i.e. that 5% of the exposed skin would be covered with lindane dust, and that 200 mg (not 1 gm) should be used to estimate the amount of dust that would cover a pair of hands.

#### 3. The Agency's PD 4 Response

No special protective clothing is assumed for this use, i.e. a short-sleeved shirt, long pants, and no gloves are worn. If protective clothing (long-sleeved shirt, long pants, and impermeable gloves) were worn, it is estimated that dermal exposure would be reduced by 80%.

As with the seed treatment use, the Agency assumes that 20%, not 5%, of the exposed skin area is covered with lindane dust. As for the amount of dust which covers 2 hands, the Agency accepts the evidence submitted by Zoecon and Edwards (submitted for the seed treatment use) that 200 mg is more correct than 1 gm.

Although not submitted as rebuttal evidence, the Agency has reestimated the frequency of use to be twice per year.

To estimate respiratory exposure during the dusting process using actual data rather than a hypothetical model, it is assumed that lindane air concentrations during the dusting process are comparable to lindane concentrations (2 mg/m$^3$) surrounding a planter box during lindane (18.75% w/w) seed treatment (Zoecon, 1980). 50% of the dust is respirable. (For explanation of this assumption, please refer to SEED TREATMENT - the Agency's PD 4 Response). A breathing rate of 1.2 m$^3$/hr for light work is assumed.

For estimating respiratory exposure to home occupants, the same assumptions were made for dog dusts as were made for dog dips, except that dogs are dusted twice a year, not once a year as with the dog dip.

## VII. BELOW-SHOULDER SPRAYS

### A. Cucurbits

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that exposure to applicators applying lindane to cucurbits would be comparable to applicator exposure in boom (row-crop) spraying of the herbicide paraquat (Staiff et al., 1975), which was 0.4 and 0.001 mg/hr for dermal and respiratory exposures, respectively. A 0.06% w/w lindane solution was assumed.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) agreed that it was reasonable to calculate exposure using the data from Staiff et al. (1975). However, he said the Agency incorrectly calculated the concentration of paraquat from the Staiff paper: the correct value being 0.13% w/w rather than 0.025%.

Edwards also said the USDA recommended dose is 1 lb. of 25% WP in 100 gallons of water per acre, not 1 lb. ai/200 gal/acre as used by the Agency in the PD 2/3.

#### 3. The Agency's PD 4 Response

No evidence was submitted to the Agency that protective clothing is routinely worn by applicators spraying lindane using row-crop equipment. If a long-sleeved shirt, long pants, and impermeable gloves were worn, the Agency estimates that dermal exposure would be reduced by 80%.

The use concentration from the Staiff (1975) study is recalculated by the Agency to be 0.14%.

The Agency agrees with Edwards that the value for the concentration of lindane used in the PD 2/3 was too high; 1 lb. of 25% WP in 100 gallons of water per acre is a better estimate (EPA, 1981b).

### B. Christmas trees - stump-slash applications

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency assumed that exposure to applicators applying lindane for stump-slash and trunk treatments, using a low-pressure back pack sprayer, would be comparable with exposure to applicators applying fenthion using directed spray for mosquito control (Wolfe et al, 1974). A use dilution of 0.5% w/w lindane was assumed for stump-slash treatment, and a 0.05% w/w lindane solution was assumed for trunk treatment. There was a seasonal correction factor of 0.32 due to reduction of body surface area exposed during the stump-slash treatment in early spring.

For estimating exposure to applicators making foliar applications to Christmas trees using hand-gun pressure sprayers, the Agency used the model of Batchelor and Walker (1954). In this study, fruit orchards were sprayed with parathion in hand-gun pressure sprayers. A 0.08% w/w lindane solution was assumed.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) disagreed with the Agency's assumption that two different types of sprayers are used. In his opinion, a grower would use a back-pack sprayer for all uses. Edwards also stated that lindane use dilutions of 0.1% for stump-slash and trunk treatments, and 0.05% for foliar treatments, would be more reasonable. Edwards agreed with the Agency's choice of Wolfe et al. (1974) as a surrogate model.

The U.S. Department of Agriculture agreed with the Agency's assumption that stump/slash applications are normally done using boom crop sprayers (refer to Appendix 1).

#### 3. The Agency's PD 4 Response

Sufficient evidence was submitted to the Agency that protective clothing is routinely worn by applicators who spray Christmas trees with lindane. Protective clothing measures incorporated into the PD 4 exposure analysis include a long-sleeved shirt, long pants, and impermeable gloves. It is estimated that these protective clothing measures reduce dermal exposure by 80%.

The Agency uses the back-pack sprayer model as a reasonable conservative model for its PD 4 estimates, since the extent of use of boom crop sprayers could not be verified, and since boom-crop sprayers would result in lower exposure than back-pack sprayers. The Agency also assumed use concentrations of 0.1% for stump-slash and trunk treatments, and 0.05% for foliar treatments.

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## VIII. PREPLANT SOIL APPLICATIONS

### A. Pineapples

#### 1. The Agency's Exposure Calculations in PD 2/3

In this use, lindane is injected into the soil with a fumigant before planting. Based on an exposure analysis for a similar use of DBCP, the Agency assumed that the primary route of exposure was by inhalation, and that at the low concentrations of pesticide applied, vapor concentration levels in air above soil were a direct function of the vapor pressure. After the lindane is injected, the field is covered with a plastic mulch. Potential for exposure depends on duties performed (equipment operator, mulch operator, or supervisor) during an assumed 14-hour working day. However, the anticipated hourly exposure associated with any of these functions was very small (approximately $5 \times 10^{-7}$ mg/hr).

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards (comment #94) disagreed with the assumption that the loss of lindane from soil is directly dependent upon its vapor pressure, as this does not take into account the absorption of lindane into organic and clay fractions of soil, which occurs rapidly and would lower volatilization considerably. Considering, however, that the "worst-case" value of $4.9 \times 10^{-7}$ mg/hr is so small, Edwards felt that it was not worth modifying EPA's PD 2/3 calculations.

#### 3. The Agency's PD 4 Response

The calculations made in the PD 2/3 remain unchanged for the PD 4.

## IX. HOUSEHOLD PRODUCTS (OTHER)

### A. Flea collars

#### 1. The Agency's Exposure Calculations in PD 2/3

The Agency made the following assumptions to estimate exposure to pet owners and home occupants during the use of lindane-treated flea collars: lindane was released at a constant rate for 6-8 weeks; because lindane (0.61%) was incorporated into the collar rather than on the surface of the collar, dermal exposure was considered to be negligible; data for 5% DDVP incorporated into cat collars could be extrapolated for lindane, i.e. the concentration of DDVP in the air of a room housing one animal wearing one 5% collar was 0.35 ug/$m^3$ (Shell Chemical Company, 1976); there was no difference in the volatility of lindane and DDVP; a dilution factor of 10 to compensate for difference between the DDVP study room (48 $m^3$) and a standard living area (480 $m^3$); a breathing rate of 1.2 $m^3$/hr; a person would be exposed 24 hours/day, 365 days/year; a lung absorption factor of 100%.

#### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, representing CIEL (comment #94), disagreed with the assumptions that lindane and DDVP volatilized at the same rate, and that a person would be exposed to such vapors for 24 hours/day, 52 weeks/year. Edwards suggested using no more than 16 hours/day, 48 weeks/year.

### 3. The Agency's PD 4 Response

The first three assumptions made in the PD 2/3 remain unchanged for the PD 4. However, the Agency reevaluated the data in the DDVP study, which gave the range of concentration of DDVP in the air of a room housing one animal with one collar to be 0.00013 - 0.0031 mg/$m^3$, with a mean value of 0.0016 mg/$m^3$ (Van Kamper et al., 1977). For the PD 4, this mean value is used.

The Agency disagrees with Edwards' comment about vapor pressure differences being significant, because for this use each chemical is incorporated into the collar and formulated to be released slowly.

The room dilution factor of 10 is retained. For this use, a factor of 3 air changes per hour is not included in the calculations, because the DDVP room where the study was conducted already had a high air exchange rate.

The Agency assumes that a person would be exposed 15 hours a day, 365 days a year, and would have a breathing rate of 0.68 $m^3$/hr. (For an explanation of these assumptions, please refer to SHELF PAPER - The Agency's PD 4 Response.) Because it is assumed that the lindane would be in a vaporized state, the 100% lung absorption factor is retained.

## B. Shelf paper

### 1. The Agency's Exposure Calculations in PD 2/3

The Agency made the following set of assumptions: inhalation was the primary route of exposure; after 105 days, 40% of the lindane had vaporized; a 12-foot roll of shelf paper, containing 15 mg lindane per $ft^2$, was used to treat three 4x4x8 meter rooms; a person had a 1.2 $m^3$/hr breathing rate; the dermal exposure was considered very small and unquantifiable (therefore no dermal exposure was assumed); exposure occured 24 hours/day, 105 days/year; one roll of lindane-treated shelf paper was used per year; and 11 million people were exposed.

### 2. Comments on the Agency's PD 2/3 Exposure Calculations

Edwards, representing CIEL (comment #94), criticized the Agency for not including air exchange rates, and for assuming continual exposure by the occupants. Rather than the Agency's hypothetical model, Edwards recommended using the data in Queen (1953), where lindane was released from a vaporizer at a rate of 1 mg/24 hrs/1300 $ft^3$ into a closed room, giving lindane air concentrations of 0.4 - 0.5 ug/l of air for 100 days. Using the Queen data and EPA's assumption that 40% of the lindane from a 12 $ft^2$ roll of shelf paper vaporized into three rooms 4x4x8 meters in size, Edwards estimated a lindane air concentration of 0.026 ug/$m^3$. He further assumed a 1.2 $m^3$/hr breathing rate, that 16 hours a day would be spent indoors, and that exposure would last 105 days.

Paper Products, Inc. (comment #93) said that the Agency should have accounted for air turnover in the treated dwelling, and suggested that the Agency use 3 air exchanges per hour as a conservative estimate (which had been used by the

Agency for other uses in the PD 2/3). Also, the formulation of its shelf paper has been changed to include the use of a new resinous binder that dissolves the lindane and holds it on the paper, with 27.12%, not 40%, volatilizing in 105 days. Concerning breathing rates, Paper Products felt it was unreasonable for the Agency to assume that a person would be engaged in light work (1.2 $m^3/hr$) for 24 hours a day, and that a breathing rate of 0.252 $m^3/hr$ was more reasonable.

Millen Industries, Inc. (comment #112) and Athena Products Corporation (comment #102) submitted identical rebuttal comments for the lindane-treated shelf paper use. They argued, based on the data contained in the report entitled "Determination of Lindane in Air of a Closed Room" (submitted to the Agency after the publication of the PD 1) that 8 air exchanges per day, and 0.000004 mg/hr for respiratory intake, would be more reasonable.

### 3. The Agency's PD 4 Response

The model in the PD 4 utilizes a study conducted on a mothproofing product not registered in the U.S. (Haag and Pruggmayer, 1981). In this study, average lindane air concentrations were measured inside a closed wardrobe (0.4 $mg/m^3$), and in the outside room air but with no ventilation (0.002 $mg/m^3$). A ratio of inside to outside concentrations is used.

In the study submitted by Millen Industries, a lindane air concentration inside a closed cabinet, 9 days after being lined with shelf paper containing 31 mg lindane/$ft^2$, was 0.4 $mg/m^3$. This value is then multiplied times the ration established in the Celamerk study to give a better estimate for the actual lindane air levels which might be expected from the shelf paper use.

The Agency agrees that a consistent air exchange rate should be used for all the indoor uses of lindane. Therefore, for the PD 4, the Agency is using 3 air changes per hour.

The issue was raised by various registrants that for home uses of lindane it was unreasonable to assume that residents would spend 24 hours a day, 365 days a year indoors. To estimate a more reasonable number, realizing that there would be many exceptions, the Agency uses an estimate of 15 hours per day (Leary et al., 1974) as representative time spent for the average resident indoors. The 365 days/year estimate was retained for the shelf paper use, for lack of evidence submitted to the contrary.

Concerning representative breathing rates for a person indoors, the Agency agrees that it is unlikely that a person would be engaged in light work for the entire 15 hours/day the Agency has assumed is spent indoors. Therefore, a more representative average breathing rate of 0.63 $m^3/hr$ (3 hours at 1.2 $m^3/hr$, and 12 hours at 0.5 $m^3/hr$) is used. This breathing rate is used where appropriate throughout the PD 4 exposure calculations.

## C. Household sprays

### 1. The Agency's Exposure Calculations in PD 2/3

Because no actual exposure data were available, the Agency made the following assumptions in estimating a person's exposure to household sprays: a coarse spray (0.1% w/w lindane) has 0.01% particles (respirable size) between 40 and

60 microns, and 0.17% between 40 and 100 microns, with 95% of the spray being deposited on surfaces; a 12,000 $ft^3$ house has 12 oz applied over a 5 minute period, once a year; there is no dermal exposure; 0.1% of the spray is respirable; there is a breathing rate of 1.2 $m^3/hr$.

### 2. Comments on the Agency's PD 2/3 Calculations

Edwards, (comment #94), agreed with the model and assumptions used by the Agency, except that Edwards assumed 50% lung absorption rather than 100%.

### 3. The Agency's PD 4 Response

A recent study was submitted to the Agency by the Penick Corporation, which measured dermal and respiratory exposures to home applicators using resmethrin formulated in a pressurized container. In the Agency's opinion, this is a reasonable model to use to estimate homeowner exposure to lindane sprays.

Unlike the PD 2/3, but consistent with the pet use assumptions, exposure to residents after using lindane household sprays is included in the PD 4 for all applicable home uses. After a household spray is used, it is assumed that there is potential for resident exposure over a three-day period, at which time all the lindane will be vaporized. All of the vaporized lindane is assumed to be respirable.

Other assumptions (please refer to SHELF PAPER - The Agency's PD 4 Response) include the following: residents spend an average of 15 hours per day indoors; there are 3 air changes per hour; an average breathing rate is 0.64 $m^3/hr$.

# APPENDIX IV:

# MUTAGENICITY TESTS OF LINDANE: SUMMARY TABLE

| STUDY TYPE | ORGANISM/TISSUE | MODE | REPORTED RESULTS | INVESTIGATORS |
|---|---|---|---|---|
| I. GENE MUTATION | Salmonella typh. | Ames | Inconclusive | Ercegovich & Rashid (1977) |
| | Salmonella typh. | Ames | TA 1538 POS at toxic doses | Rohrborn (1977) |
| | Salmonella typh. | Ames | NEG* | Lawler et al. (1979) |
| | Salmonella typh. | Ames | NEG | Purchase et al. (1978) |
| | Salmonella typh. | Ames | NEG | van Dijck & van der Voorde (1976) |
| | Salmonella typh. | Ames | "Equivocal" | Gapalaswamy et al. (1980) |
| | Saccharomyces cere. | Ames | NEG | Schubert (1969) |
| | Saccharomyces cere. | Ames | NEG | Shalin (1977) |
| | Mouse/G 46; A 21 | HMA | NEG | Buselmaier et al. (1972) |
| | Mouse/TA 1535 | HMA | POS at toxic doses | Rohrborn (1976) |
| | Drosophila melano. | SLRL | NEG | Benes and Sram (1969) |
| II. CHROMOSOME ABERRATIONS: | Human lymphocytes/ rat fibroblasts | *in vitro* | Decr. MI/ (incr. CA) | Zimonjic et al. (1981) |
| | Human lymphocytes | *in vitro* | (POS 'tid) BR at toxic doses | Tzoneva-Maneva (1971) |
| | Ch. hamster cells | *in vitro* | ('tid BR at toxic doses) | Ishidate & Odashima (1977) |
| | Rat/Bone marrow (beta-isomer) | i p | POS for CB | Shimazu et al. (1976) |
| | Ch. hamster/Bone marrow | i g | NEG (1000 ADI) | Rohrborn (1976) |

NEG = negative

APPENDIX IV: continued

| | | | | |
|---|---|---|---|---|
| | Mouse/Bone marrow, germ cells | i g | (?NEG) | Nigam et al (1981) |
| | Rat/Bone marrow | "oral" | (?NEG) | Shtannov et al. (1980) |
| | Guinea pig/Germ cells | dermal | NEG | Dikshith et al. (1978) |
| | Human lymphocytes | Exposed workers | NEG | Kiraly et al. (1979 |
| | Rat/Fetuses | DLT | (POS?) | Carey et al. (1975) |
| | Rat/Fetuses | DLT | NEG | Rohrborn (1977)d |
| | Rat/Fetuses | DLT | NEG | Reno (1976) |
| | Rat/Fetuses | DLT | NEG | Gencik (1977) |
| | Rat/Fetuses | DLT | NEG | Buselmaier et al. (1972) |
| | Rat/Fetuses | DLT | NEG | Epstein et al. (1972) |
| | Mouse/PMN's (Micronuclei) | i g | NEG | Jenssen & Ramel (1980) |
| II. DNA REPAIR | Salmonella typh. | Diff. tox. | NEG | Lawler et al. (1979 |
| | Bacillus subt. | Diff. tox. | NEG | Shirasu et al. (197 |
| | Salmonella typh. | Diff. tox. | NEG | van Dijck et al. (19 |
| | Rat thymocytes; human lymphocytes/UDS; DNA synth. | in vitro | POS at toxic doses | Rocchi et al. (1980) |
| | Transf. human cell line (VA-4)/UDS | in vitro | NEG | Ahmed et al. (1977) |
| | Rat/Mouse HPC/UDS | in vitro | NEG | Probst et al. (1981) |

## APPENDIX IV: continued

### IV. OTHER

| | | | | |
|---|---|---|---|---|
| Plant Cytology: | Algal cell division | | PCS | Jeanne (1979) |
| | Algal cell division | | PCS | Das & Singh (1978) |
| | Algal cell division | | PCS | Kar & Singh (1979) |
| | Allium cepa root tips | | PCS for c-mitoses | Nyborn (1947) |
| | Zea mays root tips | | PCS for decr. DNA synth/mitoses | Anderegg et al. (1977) |
| | Pisum sativum | | Polyploidy | Baqar et al. (1971) |
| ammalian Cells: | MO/B-16 HeLa/HESF cell lines | *in vitro* | NEG for multinucleation | deBrabander et al. (1976) |
| | Rat liver cells | *in vitro* | INCR. MI/tetraploidy | Hitachi et al. (1975) |
| ell Transfor- ation: | BHK21/WI-38/Chang | *in vitro* | NEG | Purchase et al. (1978) |

# APPENDIX V

## List of Abbreviations

| | |
|---|---|
| a.i. | active ingredient |
| CAG | Carcinogen Assessment Group |
| CFR | Code of Federal Regulations |
| CIEL | Centre International d'Etudes du Lindane - a non-profit international scientific study group on lindane, established in 1969 and organized under the laws of Belgium. Members are nine companies which manufacture lindane. |
| EPA | U.S. Environmental Protection Agency |
| FIFRA | Federal Insecticide, Fungicide and Rodenticide Act, as amended (7 U.S.C. 136 et seq.) |
| FR | Federal Register |
| FY | Fiscal Year |
| PD | Position Document |
| ppm | parts per million |
| RPAR | Rebuttable Presumption Against Registration - a process, carried out by the Office of Pesticide Programs in EPA, to gather and analyze data on the risks and benefits of registered pesticides. |
| SAP | Scientific Advisory Panel |
| USDA | U.S. Department of Agriculture |
| wp | wettable powder |
| w/w | weight per weight |
| ug | microgram |

## COMMENT REFERENCES*

(3000/10c)

| comment number | submitted by |
|---|---|
| 91 | National Association of Wheat Growers |
| 93 | Paper Products, Inc. |
| 94 | Centre International d'Etudes du Lindane |
| 102 | Athena Products Corporation |
| 104-109 | Trout Unlimited |
| 112 | Millen Industries, Inc. |
| 116 | Janette Sherman, M.D. |
| 134 | Chapman Chemical Company |

* This list includes only those comments received by EPA following issuance of PD 2/3 and cited in PD 4. All comments received by EPA are available for review in the public file located in the Document Control Office, room 106 East Tower, 401 M Street, S.W., Washington, D.C. 20460.

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# Policy Group

## Lindane Briefing Paper

The Project Support Team disagrees as to the appropriate regulatory response to the high dietary exposure of lindane. The team agrees on the appropriate regulatory response for applicator risks associated with uses on commercial ornamentals, avocadoes, pecans, forestry and hardwood logs. However, the team believes that the regulatory response may be controversial and requests Policy Group review and confirmation of its position.

### Issues to be Addressed by the Policy Group

Three issues need to be addressed by the Policy Group:

1. Whether or not to initiate regulatory action and what that action should be for lindane food uses, considering the fact that the TMRC is 15,766% of the MPI.
2. Whether to express strong concern about the potential applicator risks from the hardwood lumber use, but withhold a Special Review decision until the acute inhalation study is reviewed and the chronic rat study is conducted and reviewed.
3. Whether to support the PD 4 position to retain the uses for pecans, avocadoes, ornamentals, and forestry.

### Background

Lindane is an insecticide used primarily for seed treatment, livestock and hardwood lumber. These three uses comprise approximately 87% of the total usage. Other uses include food, non-food outdoor, and indoor uses.

Lindane was RPARed by the Agency for its potential to cause cancer. The triggers for fetotoxicity/teratogenicity and reproductive effects were successfully rebutted. Its potential to cause blood dyscrasias could not be confirmed with the data on hand. The trigger for acute toxicity to aquatic wildlife was withdrawn because lindane is no longer registered for uses involving direct aquatic application.

The RPAR decision resulted in the cancellation of lindane smoke fumigation devices. Protective clothing was required for applicators for ornamentals, avocadoes, pecans, livestock, forestry, Christmas trees, crawl space treatments, and dog dips and dusts. The registrants agreed to conduct special mutagenicity tests for lindane to enable an assessment of its genotoxic potential.

Subsequently, lindane was included in a suit by NRDC requiring the Agency to reassess its final decision. In compliance with the suit, the Agency agreed to conduct a comprehensive reassessment of this chemical and publish that reassessment in the form of a Registration Standard by September 30, 1985. This review is to include an evaluation of a three month subchronic study of lindane which was received shortly before the RPAR was completed and an assessment of its genotoxic potential based on the new mutagenicity studies.

As part of the Registration Standard review, HED asked CAG to reassess the lindane oncogenicity in mice given the results of the new mutagenicity tests which confirm that lindane has little or no genetic activity. Using the new cancer guidelines, CAG has classified lindane as a B2-C oncogen (i.e., in between the B2 and C categories of the guidelines). HED believes the weight of evidence is closer to a "C" class than a "B2" dose-response.

## Issue 1: Food Uses

There are over 40 registered uses of lindane for food. By far the most significant are seed treatments (48% of all use) and livestock (20% of all use). Other major uses include pecans (3%), pineapples (2%), cucurbits (1%), and avocadoes (1%). Many of the registered uses are not active.

Using the conventional method of total maximum residue contribution (TMRC), a 1.4189 mg/day intake can be computed. Because of inadequate analytical methods, incomplete characterization of the nature of the residues in plants and animals, and lack of a good chronic feeding study, the tolerances are virtually unsupported by residue data meeting current standards and a conventional ADI cannot be established. Additional residue data and a rat chronic feeding study will be required under this standard to support the existing tolerances.

For the present time the best available data for determining a provisional acceptable daily intake (PADI) is the new subchronic 90 day feeding study in the rat which was received shortly before the RPAR was completed. This study, which meets core guideline criteria, showed that lindane caused toxic changes primarily in the kidneys but aslso in the liver of male and female rats. Renal changes were irreversible with a NOEL of 4 ppm in the diet equivalent to 0.3 mg/kg bodyweight/day. Using this latter value and a customary safety factor of 2,000 for a subchronic study, the PADI is 0.00015 mg/kg/day and the maximum permissible intake for a 60 kg person is 0.009 mg/day. Based upon a TMRC of 1.4189 mg/day/1.5 kg of diet the percent of the MPI used up is 15,766%. It is this high percentage of MPI used up that is of major concern. At this MPI the cancer risk is about $10^{-4}$.

Both the PD 2/3 and 4 used figures derived from FDA Total Diet Composites rather than the TMRC method of summing the established tolerances. Certain members of the Support Team believe that FDA's Total Diet Composites figures should also be used now to estimate dietary exposure since they would more accurately reflect actual residues of lindane in foodstuffs. In addition, FDA has concluded that regulatory compliance samples as well as Total Diet Composite Samples, collected over several years, indicate that dietary intakes of lindane in adults, infants and toddlers are within acceptable limits. If market basket figures are used, then the average daily consumption of lindane is 0.000002 mg/kg and the cancer risk is $2 \times 10^{-6}$.

NRDC disagreed with the Agency's estimate of dietary exposure with respect to the use of FDA Market Basket Survey data in PD 4 and is likely to disagree again if the Agency uses this method to evaluate lindane residues under the Registration Standard.

These dietary risk estimates do not reflect the seed treatment uses, since these uses were previously considered non-food uses and no tolerances exist for them. Present Agency policy now categorizes seed treatment uses as food uses unless radio-labeled studies (being required under the standard) show that no residues remain in the edible portion of the food crop. While there is expectation that residues in edible portions are likely to be minimal, any additional tolerances which are required to support the seed treatment uses would further inflate the percent of the MPI being used.

HED has looked at possible ways to reduce the percent of MPI being used. If a good chronic study was already available and the conventional safety factor of 100 were used (rather than the 2,000 being used for the subchronic study), the MPI being used would be 788%. Selectively adjusting the TMRC to reflect percent of crop treated would also reduce the percent of MPI used since many of the tolerances are not being used at all and others (such as the livestock uses) are not used on all animals. Further reductions would occur if tolerances were lowered to reflect actual residues. Whether these actions would bring the MPI being used down to 100%, particularly with the addition of the seed treatment uses, is questionable.

Members of the Support Team disagree as to which of the following regulatory options should be chosen.

a. Take no regulatory action now. After receipt and review of future residue and toxicology data (approximately four years from now), decide on regulatory action that is commensurate with the studies' results. Under this option the Agency publicly acknowledges the fact that current FDA Market Basket Data should be used to evaluate pesticide residues in the diet of the general population, as it did in the PD-4, and will not consider any further regulatory action that might be necessary to reduce dietary exposure and risk until all the toxicology and residue data needed to conduct a complete tolerance reassessment are submitted and reviewed. This option means a delay in initiating the public comment inherent in the Special Review process for at least four years until the necessary data are submitted.

b. Initiate now a benefit assessment and a Special Review and use this process to reach a regulatory decision.

Under this option the public, NRDC and user groups are informed of the potential high dietary exposure in light of the Agency's concern that lindane is a oncogen and may cause other chronic effects. This gives users and industry an advance notice to consider alternatives and delete those uses of marginal market importance. However, this option may waste resources if the future data indicate that dietary risk are acceptable.

Issue 2: Hardwood Lumber Use

The PD 4 calculated an exposure to hardwood lumber applicators of $10^{-4}$, using protective clothing, based on the cancer risk. This risk level was considered acceptable given that benefits from the use are significant, the number of applicators is low (1,000-2,000), and the primary alternative (endosulfan) has potential equal or greater risks associated with it.

Based on the subchronic rat study kidney effects (.3 mg/kg/day), a Margin of Safety (MOS) has been calculated at 230. Given that workers may be exposed for 200 days per year, this margin of safety may not be adequate. However, without additional data, a regulatory decision cannot be reached. Further information on inhalation toxicity is needed to characterize risk from that route. (An inhalation study has been submitted but has not yet been reviewed. The summary of the study, if accurate, shows effect levels which would not raise concern. However, the entire study must be reviewed to confirm those results. The study is in German and must be translated. Therefore, further review will not be available by the time the Registration Standard is issued.) Also, the chronic rat study being required will help determine whether kideny effects result from long term exposure and whether these effects are reversible.

Based on this information, the team agreed to express concern about potential risk from this use but to defer a Special Review decision until the inhalation study is reviewed and the chronic rat study is received and reviewed. The team requests confirmation of this position from the Policy Group.

Issue 3: Ornamental, Avocado, Pecan, and Forestry Uses

The PD 4 contained tabluations of risk associated with non-dietary exposures to applicators and other bystanders. The forestry use was considered a subchronic exposure (30 days per year) and the ornamental, avocado, and pecan uses were considered an acute exposure (only a few days per year).

In light of the new subchronic toxicity data in rats, the team was faced with the possibility of recalculating the MOS based upon kidney effects (.3 mg/kg/day) for these uses. However, considering the type and duration of exposure and the fact that lindane accumulates in tissues like other chlorinated hydrocarbons, the team decided that the PD 4 margins of safety based on acute and chronic effects were more representative of the exposure risks to these uses. Therefore, the team agrees that the existing MOS and cancer risks for these uses should remain unchanged. The team reconfirms the determination reached in the PD 4 that, although the risks are high from these uses ($10^{-4}$), the benefits and labeled protective measures offset these risks and no further regulatory action is necessary.

Because of expected NRDC opposition to this conclusion, the team requests Policy Group confirmation of this decision.